Meta-analyses of controlled clinical trials for rare AEs

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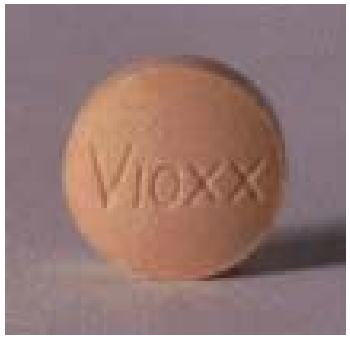
Background

- Increasingly regulators, particularly FDA, are asking Sponsors for the evaluation of all available clinical data in relation to the occurrence of some AE of concern.
- Often this is often triggered on just a handful of events, or some small unexpected imbalance or ‘signal’ in a large trial
- High profile cases such as Vioxx and Avandia provide examples where systematic evaluation of all controlled clinical trial was undertaken.
- New diabetes guidance and requirement regarding CV risk to be ruled out



Background

- Increasing number of requests to evaluate AE data for some ‘signal ‘of concern.
- However, the approach to the aggregation of data across trials varying considerably from project to project, with little common thread of statistical and clinical efficiency or consistency.
- Therefore a simple, statistically consistent and clinically meaningful approach to the evaluation, presentation and aggregation of rare AE data across trials was laid down.
- Used as standard approach for responding to regulators and to aid assessment of potential risk within the business.

Methods

- Stratified relative risk assessment via Mantel-Haenszel (M-H)
- M-H stratified, exposure-weighted event rate estimates. Crude, pooled estimates to be avoided.
- Supplementary provision of difference in stratified M-H event rates to account for all trials, including those with no events.
- Descriptive use of Bayesian credibility intervals for an individual trial when there are very few, if any, events.
- Use of StatXact PROCS for SAS to provide exact inference where necessary.

Relative risk assessment via M-H

- Suppose there are k trials, each with a drug and a control arm denoted as treatments 1 and 2. For treatment j in the ith trial patient-years exposure is T_{ij} and E_{ij} events are observed. Let $T_{i\bullet} = T_{i1} + T_{i2}$ and $E_{i\bullet} = E_{i1} + E_{i2}$ denote total exposure and total events respectively in the ith trial.

- If counts are assumed to follow a Poisson distribution with parameter λ_{ij}, then the relative risk within the ith trial is given by $R_i = \lambda_{i1} / \lambda_{i2}$.

- Under H_0: $R_1 = R_2 = \ldots = R_k = R$ the stratified Mantel-Haenszel (MH) estimate[1] and variance[2] of the common relative risk is

$$\hat{R}_{M-H} = \frac{\sum_{i=1}^{k} \frac{E_{i1}T_{i2}}{T_{i\bullet}}}{\sum_{i=1}^{k} \frac{E_{i2}T_{i1}}{T_{i\bullet}}} \qquad \hat{V}\left[\log\left(\hat{R}_{M-H}\right)\right] = \frac{\sum_{i=1}^{k} T_{i1}T_{i2}E_{i\bullet} / T_{i\bullet}^2}{\hat{R}_{M-H}\left\{\sum_{i=1}^{k} \frac{T_{i1}T_{i2}E_{i\bullet}}{T_{i\bullet}\left(T_{i2} + T_{i1}\hat{R}_{M-H}\right)}\right\}^2}$$

1. Breslow and Day; 2.Robins, Breslow and Greenland

M-H stratified, exposure-weighted event rate estimates

- $\hat{R}_{M-H} = U_1 / U_2$, where $U_j = \dfrac{\sum_{i=1}^{k} w_i \hat{\lambda}_{ij}}{\sum_{i=1}^{k} w_i}$ with $\hat{\lambda}_{ij} = E_{ij} / T_{ij}$ and $w_i = 2/\left(T_{i1}^{-1} + T_{i2}^{-1}\right)$

- U_j is therefore the MH exposure weighted event rate for treatment j across trials.

- Note that (i) even trials with zero events contribute to the denominator in U_j and (ii) since $\hat{R}_{M-H} = U_1 / U_2$ by definition, the U_j's are fully consistent with the overall MH relative risk estimate. Thus, the U_j's are far preferable to the usual crude incidence rates across trials, crude rate = $\sum_{i=1}^{k} E_{ij} / \sum_{i=1}^{k} T_{ij}$,

  since $R_{crude} = \dfrac{\sum_{i=1}^{k} E_{i1} / \sum_{i=1}^{k} T_{i1}}{\sum_{i=1}^{k} E_{i2} / \sum_{i=1}^{k} T_{i2}} \neq \hat{R}_{M-H}$

M-H event rate CIs and event rate difference

- Since $\hat{V}ar[U_j] = \dfrac{\sum_{i=1}^{k} w_i^2 \dfrac{E_{ij}}{T_{ij}^2}}{\left(\sum_{i=1}^{k} w_i\right)^2}$ and $\hat{V}ar[\log(U_j)] = \dfrac{1}{U_j^2} Var[U_j] = \dfrac{\sum_{i=1}^{k} w_i^2 \dfrac{E_{ij}}{T_{ij}^2}}{\left(\sum_{i=1}^{k} w_i \dfrac{E_{ij}}{T_{ij}}\right)^2}$

  then an approximate 95% CI for U_j is given by $U_j \times e^{\pm 1.96 * \sqrt{\hat{V}ar[\log(U_j)]}}$

  and an approximate 95% CI for the difference in event rates, $U_1 - U_2$, is given by

  $$U_1 - U_2 \pm 1.96 \times \sqrt{\hat{V}ar[U_1] + \hat{V}ar[U_2]}$$

Bayesian credibility intervals for individual trials

- Assuming an non-informative prior, the posterior distribution for λ_1 / λ_2 is given by

$$\left[\frac{E_2+1}{E_1+1}\times\frac{T_1}{T_2}\right]\frac{\lambda_1}{\lambda_2}\sim F\left(2(E_1+1),2(E_2+1)\right)$$

- The credibility interval for λ_1 / λ_2 is therefore given by

$$\left\{\left[\frac{E_1+1}{E_2+1}\times\frac{T_2}{T_1}\right]\times F_{2E_1+2,2E_2+2}(0.025)<\frac{\lambda_1}{\lambda_2}<\left[\frac{E_1+1}{E_2+1}\times\frac{T_2}{T_1}\right]\times F_{2E_1+2,2E_2+2}(0.975)\right\}$$

  and is calculable even when both E_1 and E_2 are zero. This interval rapidly coincides with the conventional maximum likelihood confidence interval for the relative risk as E_1 and E_2 increase.

- A point estimate for the relative risk can be provided by the median of the posterior distribution as

$$R_{Bayes}=\left[\frac{E_1+1}{E_2+1}\times\frac{T_2}{T_1}\right]\times F_{2E_1+2,2E_2+2}(0.5)$$

Bayesian credibility intervals for individual trials

- The posterior distribution for λ_i is Gamma(T_i, E_i+1), hence the credibility interval for λ_i is therefore given by

$$\text{Gamma}_{T_i, E_i+1}(0.025) < \lambda_i < \text{Gamma}_{T_i, E_i+1}(0.975)$$

  and is again calculable when E_i is zero.

- A point estimate for the even rate can be provided by the median of the posterior distribution as

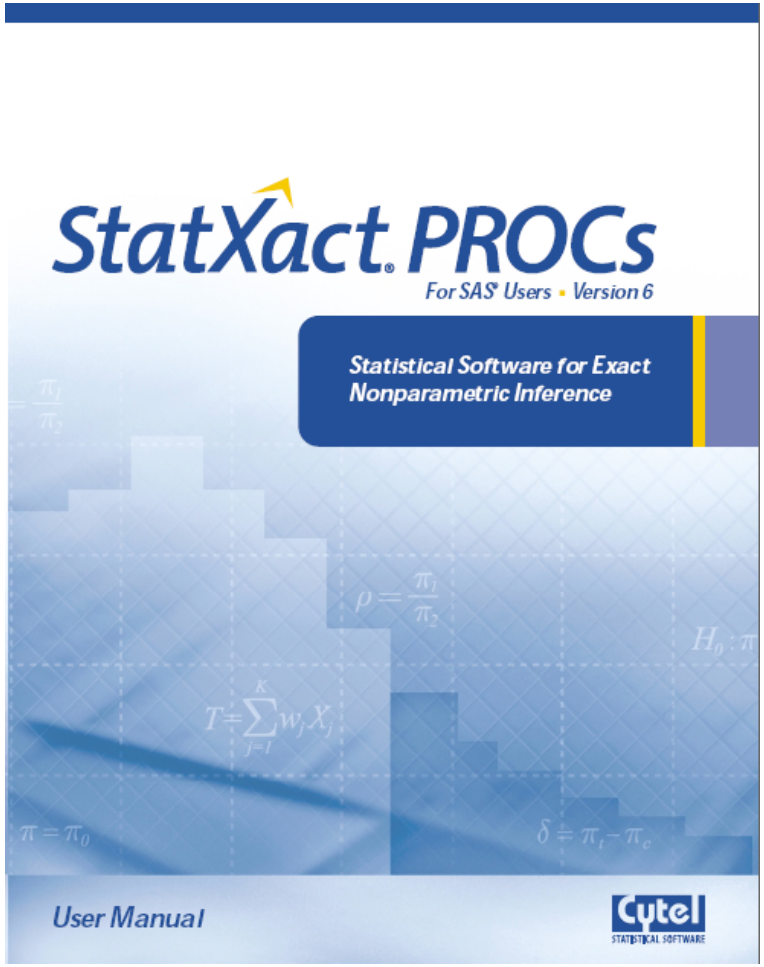
$$\lambda_{\text{Bayes},i} = \text{Gamma}_{T_i, E_i+1}(0.5)$$

  Also, note that

$$R_{\text{Bayes}} \cong \frac{\lambda_{\text{Bayes},1}}{\lambda_{\text{Bayes},2}}$$

StatXact®6 PROCS for SAS® to provide exact inference where necessary

- Excellent procedure and User Manual.
- Exact inference for a very wide range of problems.
- M-H RR, M-H odds ratio, exact binomial CIs, etc.
- Must have for statistical evaluation of rare events across trials.



Example #1

	Drug			control				
Trial	N	Events	Exposure (pt-yrs)	N	Events	Exposure (pt-yrs)	Crude event rate per 1000 pts drug	Crude event rate per 1000 pts control
1	135	0	59.5	133	1	35.3	0.0	28.3
2	275	6	100.9	155	2	36.1	59.5	55.4
3	83	2	31.1	86	1	25.7	64.3	38.9
4	275	7	118.1	141	0	48.6	59.3	0.0
5	242	0	92.8	253	0	73.4	0.0	0.0
6	129	0	53	66	1	18.1	0.0	55.2
7	135	0	47.8	33	0	5	0.0	0.0
8	275	0	121.3	131	0	34.7	0.0	0.0
9	129	3	128.9	121	3	120.9	23.3	24.8
10	130	1	90.9	63	0	19.5	11.0	0.0
11	60	1	52.4	63	0	20.9	19.1	0.0
12	734	20	948.6	179	3	37.2	21.1	80.6
Overall	**2602**	**40**	**1845.3**	**1424**	**11**	**475.4**	**21.7**	**23.1**

Typical analysis: Crude event rates by arm and overall M-H stratified RR estimate

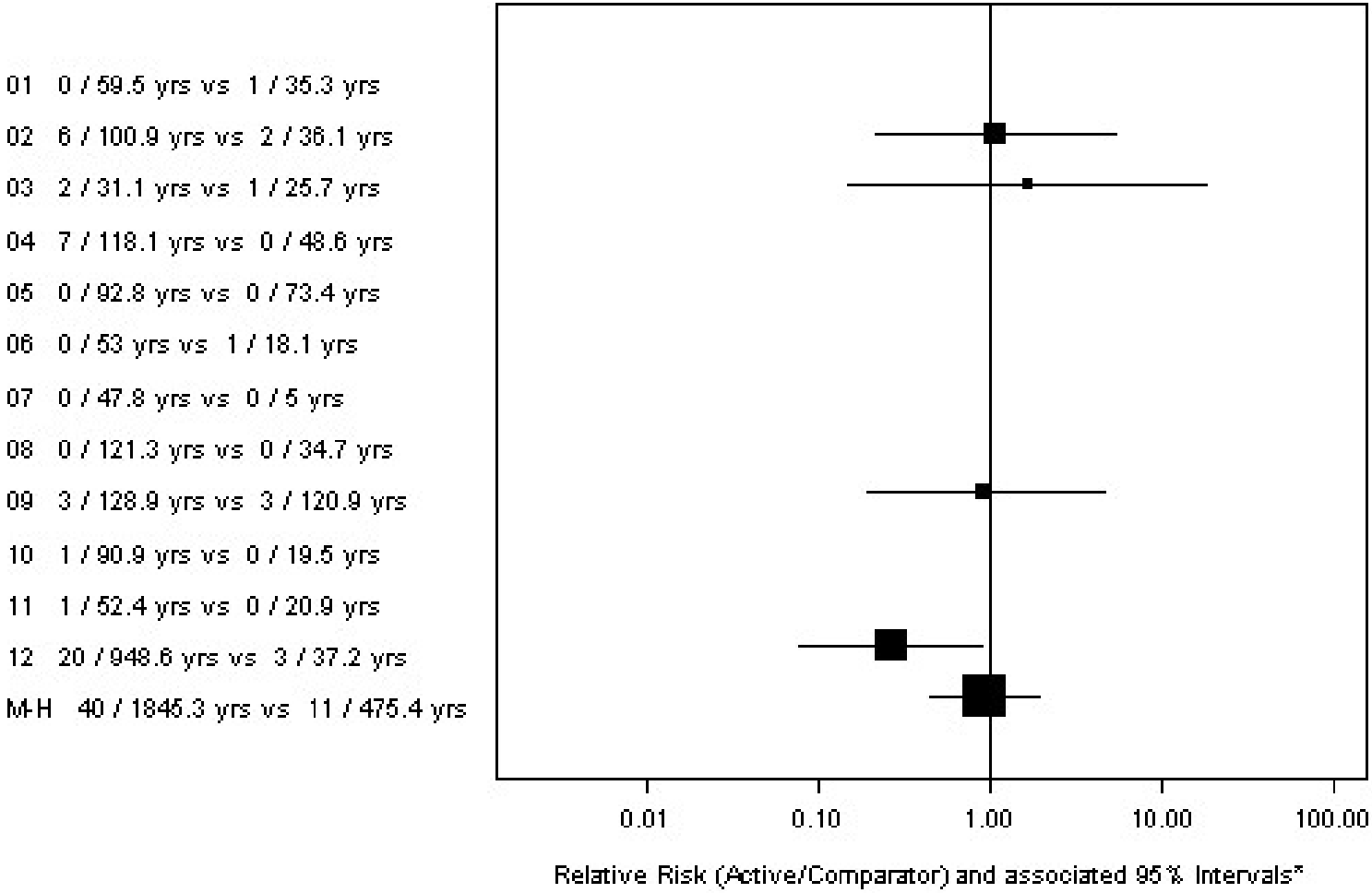
	Drug event rate per 1000 pts and 95% CI	Control event rate per 1000 pts and 95% CI
	21.7 (15.9, 29.6)	23.1 (12.8, 41.8)
MH RR and 95% CI	0.92 (0.44, 1.92)	
MH risk difference and 95% CI	-2.03 (-20.0, 15.9)	

But $\frac{21.7}{23.1} \neq 0.92$ and $21.7 - 23.1 \neq -2.0$

Typical analysis: CIs for individual trials

	Drug			control					
Trial	N	Events	Exposure (pt-yrs)	N	Events	Exposure (pt-yrs)	Crude event rate per 1000 pts drug	Crude event rate per 1000 pts control	RR and 95% CI
1	135	0	59.5	133	1	35.3	0.0	28.3	0
2	275	6	100.9	155	2	36.1	59.5	55.4	1.07 (0.22, 5.32)
3	83	2	31.1	86	1	25.7	64.3	38.9	1.65 (0.15, 18.23)
4	275	7	118.1	141	0	48.6	59.3	0.0	inf
5	242	0	92.8	253	0	73.4	0.0	0.0	inf
6	129	0	53	66	1	18.1	0.0	55.2	0
7	135	0	47.8	33	0	5	0.0	0.0	inf
8	275	0	121.3	131	0	34.7	0.0	0.0	inf
9	129	3	128.9	121	3	120.9	23.3	24.8	0.94 (0.19, 4.65)
10	130	1	90.9	63	0	19.5	11.0	0.0	inf
11	60	1	52.4	63	0	20.9	19.1	0.0	inf
12	734	20	948.6	179	3	37.2	21.1	80.6	0.26 (0.08, 0.88)

Typical analysis: CIs for individual trials



Recommended analysis: M-H stratified event rates by arm and overall M-H stratified RR estimate

	Drug event rate per 1000 pts and 95% CI	Control event rate per 1000 pts and 95% CI
	23.03 (15.3, 34.7)	25.06 (13.6, 46.1)
MH RR and 95% CI	0.92 (0.44, 1.92)	
MH risk difference and 95% CI	-2.03 (-20.0, 15.9)	

Now $\frac{23.03}{25.06} = 0.92$ and 23.03 – 25.06 = -2.03

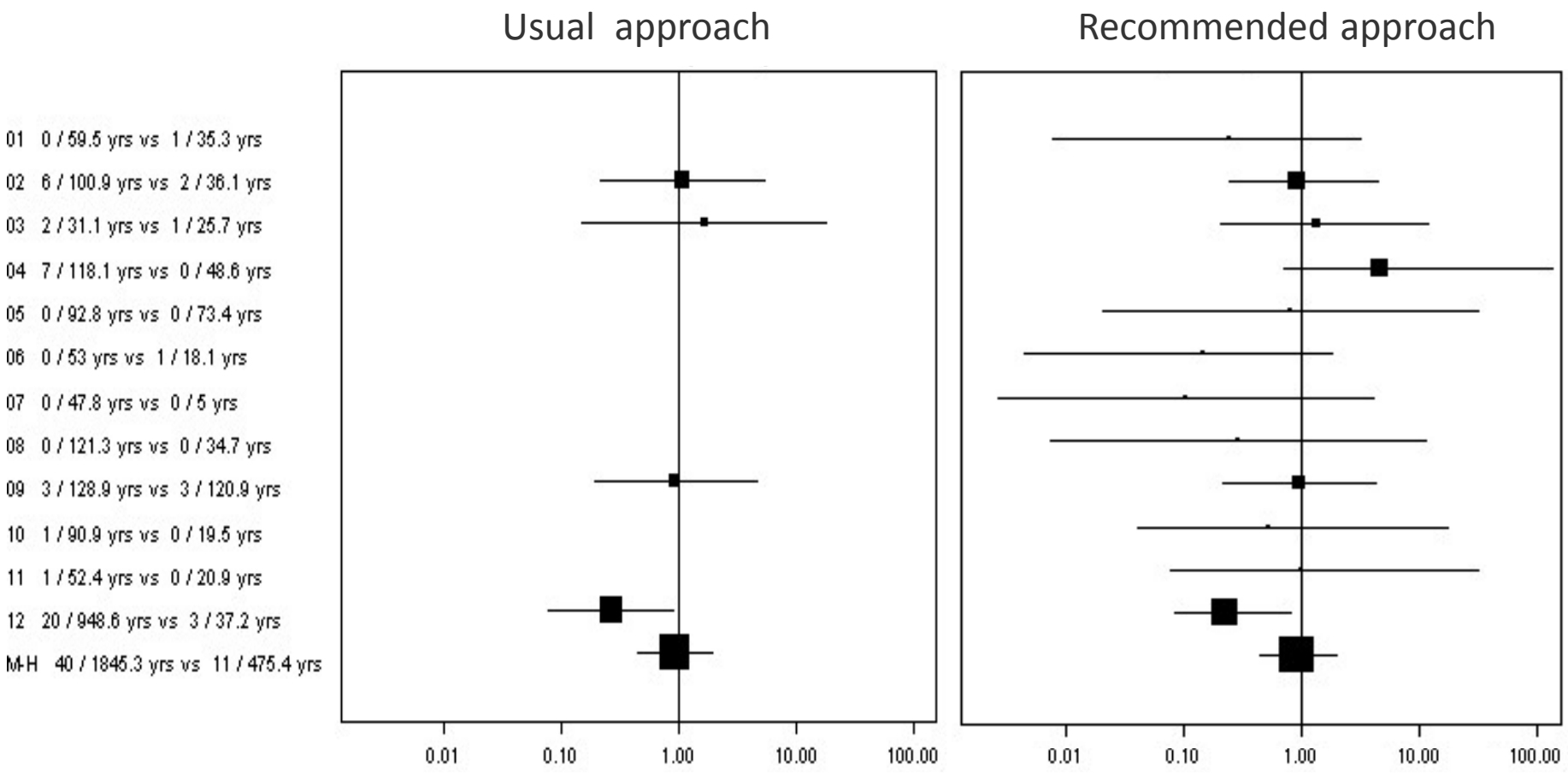
Bayesian CIs for individual trials

	Drug			control					
Trial	N	Events	Exposure (pt-yrs)	N	Events	Exposure (pt-yrs)	Crude event rate per 1000 pts drug	Crude event rate per 1000 pts control	Bayesian RR estimate and 95% CI
1	135	0	59.5	133	1	35.3	0.0	28.3	0.25 (0.01, 3.16)
2	275	6	100.9	155	2	36.1	59.5	55.4	0.89 (0.24, 4.42)
3	83	2	31.1	86	1	25.7	64.3	38.9	1.32 (0.20, 11.40)
4	275	7	118.1	141	0	48.6	59.3	0.0	4.55 (0.70, 129.83)
5	242	0	92.8	253	0	73.4	0.0	0.0	0.79 (0.02, 30.85)
6	129	0	53	66	1	18.1	0.0	55.2	0.14 (0.00, 1.82)
7	135	0	47.8	33	0	5	0.0	0.0	0.10 (0.00, 4.08)
8	275	0	121.3	131	0	34.7	0.0	0.0	0.29 (0.01, 11.16)
9	129	3	128.9	121	3	120.9	23.3	24.8	0.94 (0.21, 4.16)
10	130	1	90.9	63	0	19.5	11.0	0.0	0.52 (0.04, 16.84)
11	60	1	52.4	63	0	20.9	19.1	0.0	0.96 (0.07, 31.31)
12	734	20	948.6	179	3	37.2	21.1	80.6	0.22 (0.08, 0.79)

Bayes event rates for drug and control with CIs

	Drug event rate - Bayes estimate			Control event rate - Bayes estimate				
Trial	Posterior median	lower 95% CI	upper 95% CI	Posterior median	lower 95% CI	upper 95% CI	Ratio drug:control event rates	R_{Bayes}
1	11.6	0.4	62.0	47.5	6.9	157.8	0.25	0.25
2	66.1	27.9	129.4	74.1	17.1	200.1	0.89	0.89
3	86.0	19.9	232.3	65.3	9.4	216.8	1.32	1.32
4	64.9	29.2	122.1	14.3	0.5	75.9	4.55	4.55
5	7.5	0.3	39.8	9.4	0.3	50.3	0.79	0.79
6	13.1	0.5	69.6	92.7	13.4	307.8	0.14	0.14
7	14.5	0.5	77.2	138.6	5.1	737.8	0.10	0.10
8	5.7	0.2	30.4	20.0	0.7	106.3	0.29	0.29
9	28.5	8.5	68.0	30.4	9.0	72.5	0.94	0.94
10	18.5	2.7	61.3	35.5	1.3	189.2	0.52	0.52
11	32.0	4.6	106.3	33.2	1.2	176.5	0.97	0.96
12	21.8	13.7	32.6	98.7	29.3	235.7	0.22	0.22

Comparing approaches



Example #2: Event A

Trial	drug events	drug exposure (pt-yrs)	Control events	control exposure (pt-yrs)	Crude event rate per 10000 pts drug	Crude event rate per 10000 pts control
#1	2	7245	4	24678	2.8	1.6
#2	1	9677	10	111914	1.0	0.9
#3	7	6218	22	21470	11.3	10.2
#4	3	6784	8	8884	4.4	9.0
Total	**13**	**29924**	**44**	**166946**	**4.34**	**2.64**

1.65

MH RR and 95% CI = 0.95 (0.51, 1.76)

Example #2: Event B

Trial	drug events	drug exposure (pt-yrs)	Control events	control exposure (pt-yrs)	Crude event rate per 10000 pts drug	Crude event rate per 10000 pts control
#1	0	7245	3	24678	0.0	1.2
#2	0	9677	5	111914	0.0	0.4
#3	1	6228	3	21504	1.6	1.4
#4	0	6784	2	8884	0.0	2.3
Total	**1**	**29934**	**13**	**166980**	**0.33**	**0.78**

MH RR and 95% CI = 0.30 (0.04, 2.15)

0.43

Example #2: Event A

Serious Event A

Trial	drug events	drug exposure (pt-yrs)	Control events	control exposure (pt-yrs)	Event rate per 10000 pts drug	Event rate per 10000 pts control
#1	2	7245	4	24678	2.8	1.6
#2	1	9677	10	111914	1.0	0.9
#3	7	6218	22	21470	11.3	10.2
#4	3	6784	8	8884	4.4	9.0
Total	**13**	**29924**	**44**	**166946**	**4.14 (2.39, 7.17)**	**4.36 (3.14, 6.06)**

MH RR and 95% CI = 0.95 (0.51, 1.76)

MH risk difference and 95% CI = -0.22 (-2.91, 2.47)

Example #2: Event B

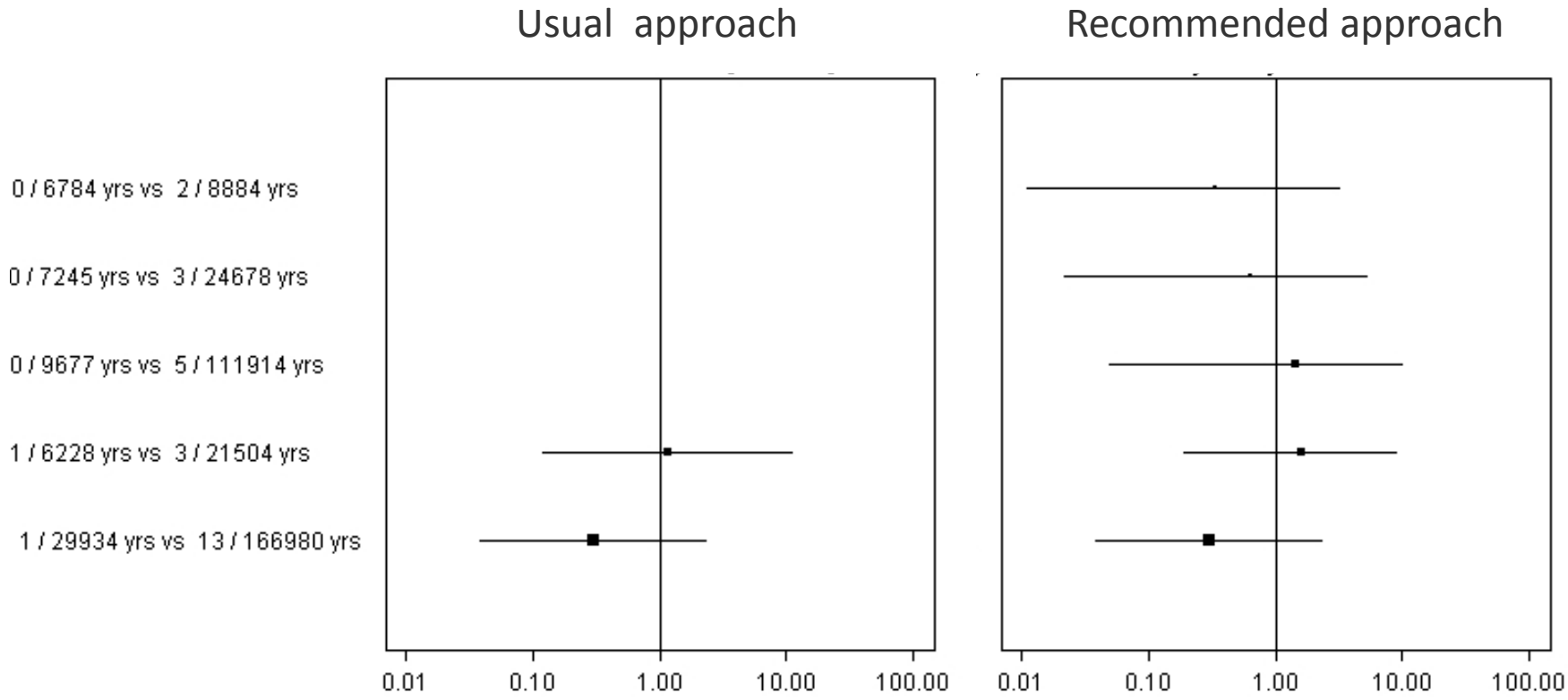
Serious Event B

Trial	drug events	drug exposure (pt-yrs)	Control events	control exposure (pt-yrs)	Event rate per 10000 pts drug	Event rate per 10000 pts control
#1	0	7245	3	24678	0.0	1.2
#2	0	9677	5	111914	0.0	0.4
#3	1	6228	3	21504	1.6	1.4
#4	0	6784	2	8884	0.0	2.3
Total	**1**	**29934**	**13**	**166980**	**0.33 (0.05, 2.37)**	**1.33 (0.60, 2.13)**

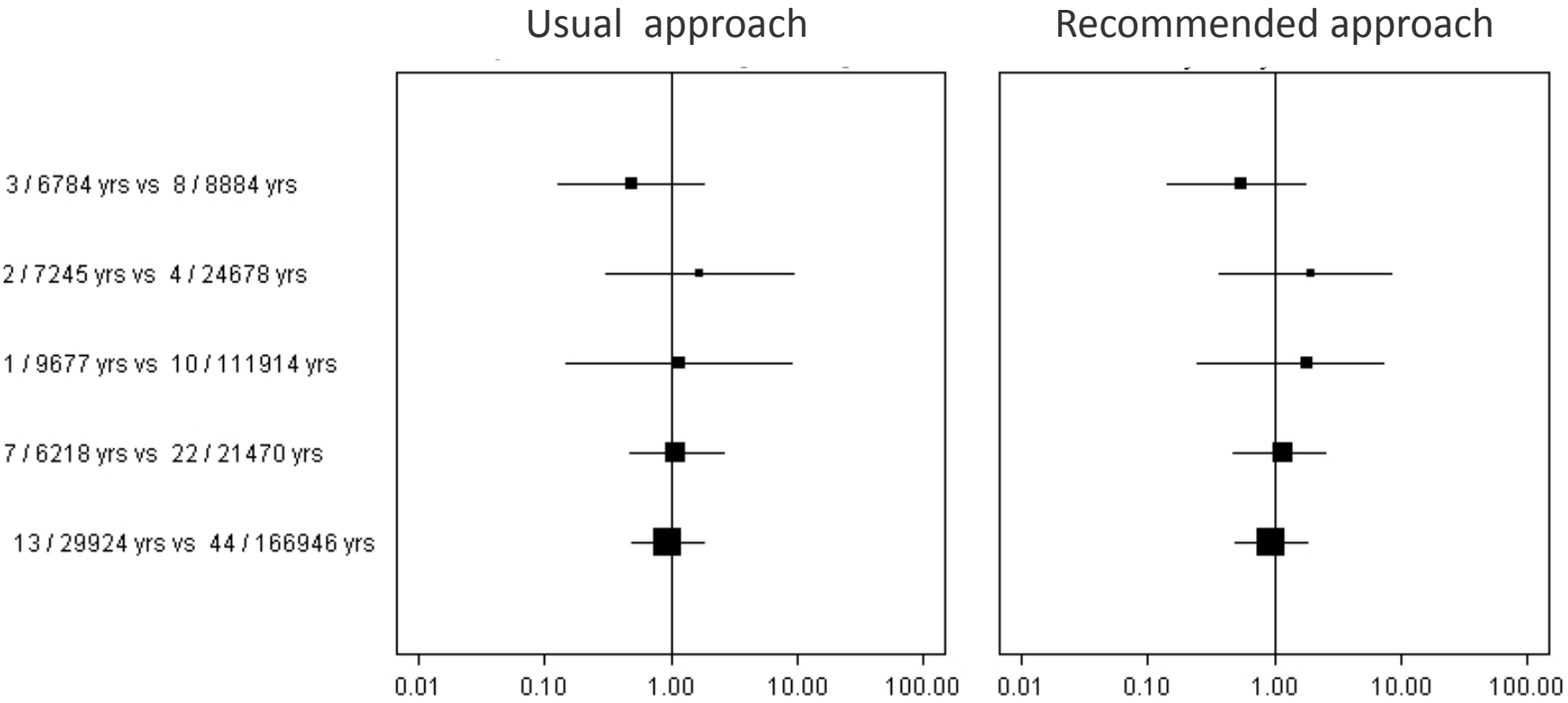
MH RR and 95% CI = 0.30 (0.04, 2.15)

MH risk difference and 95% CI =-0.79 (-1.76, 0.17)

Example #2: Event A



Example #2: Event B



No Increase in the Risk of Asthma-related Hospitalization

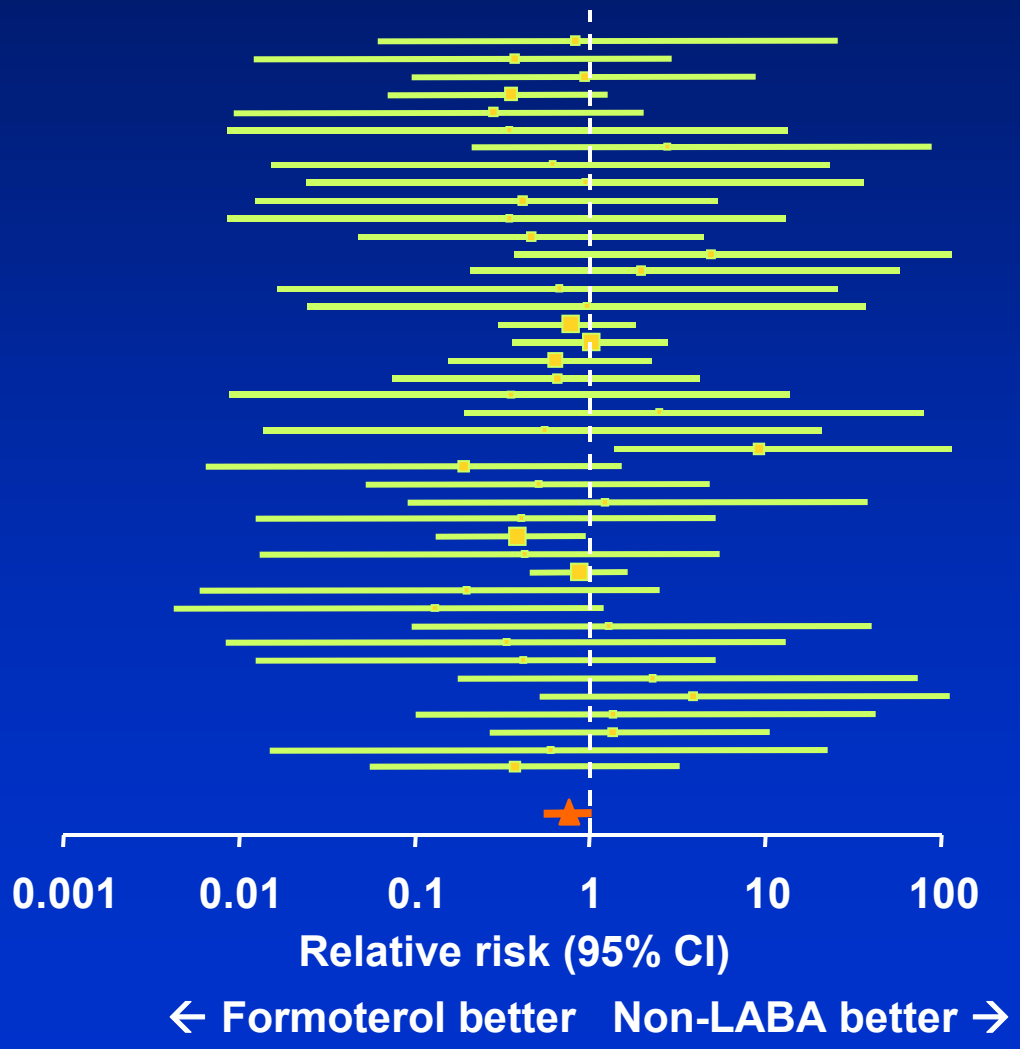
Overall Trial Data (N = 23,510)

	Formoterol exposed	Non-LABA exposed
Patients, n	13,542	9968
Total exposure (1000 treatment-yr)	6.49	4.92
Patients with ? 1 asthma-related hospitalization, n (%)	78 (0.58)	83 (0.83)
Asthma-related hospitalizations/ 1000 patients/yr	12.05	16.40
Relative risk (95% CI)	0.73 (0.54, 1.01)	
Rate difference (95% CI)	–4.35 (–8.87, 0.18)	

Adapted from Table 3 and 7 AstraZeneca Briefing Document

No Increase In the Risk of Asthma-Related Hospitalization

Overall Trial Data (N = 23,510), 42 Trials

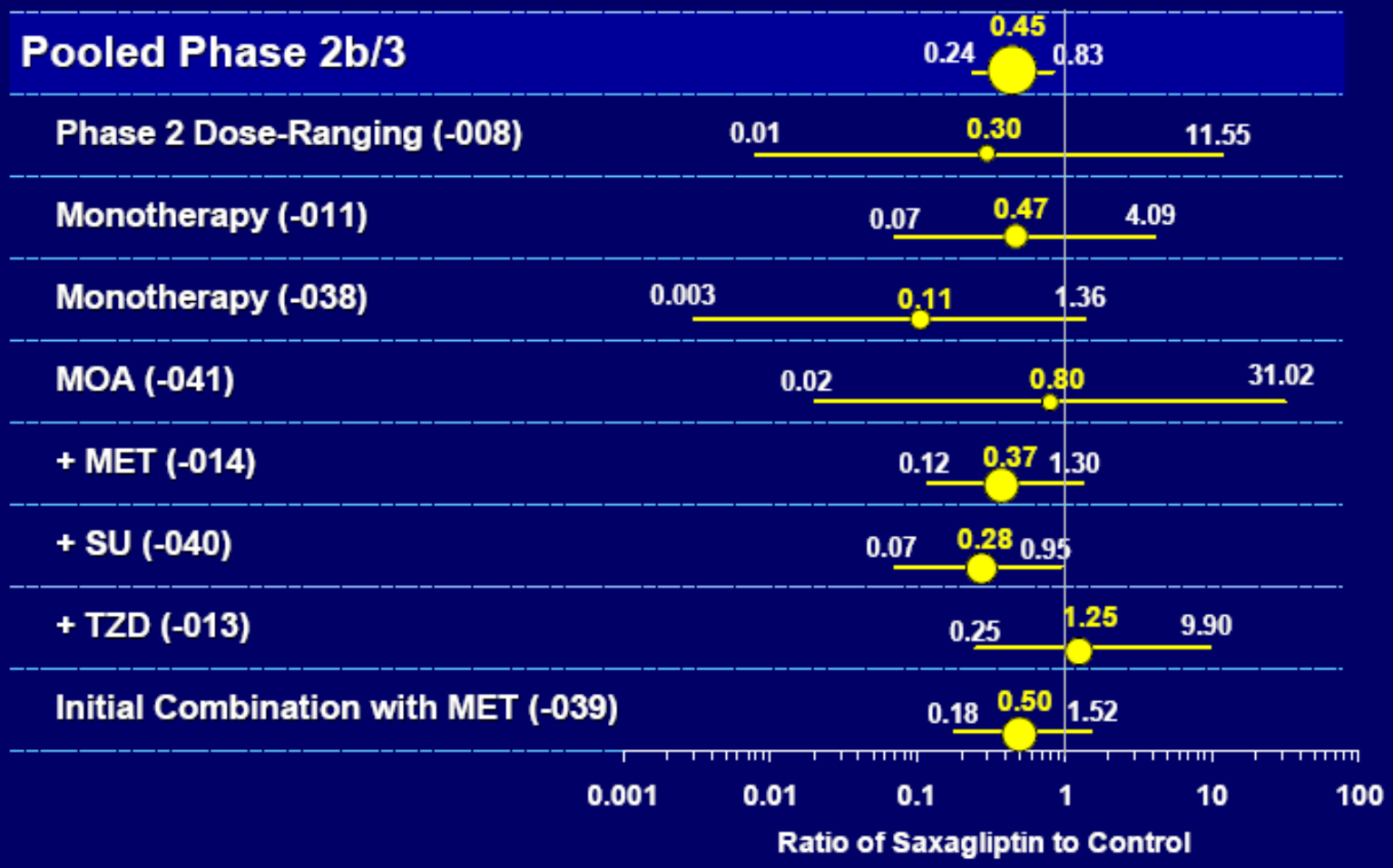


Relative risk (95% CI)
0.73 (0.54, 1.01)

Rate difference (95% CI)
–4.35 (–8.87, 0.18)

Adapted from Figure 7
AstraZeneca Briefing Document

Incidence Rate Ratio of Sponsor-defined Primary MACE



Saxagliptin Better | Control Better

Data represent point estimate and 95% CI.
Size of point estimate is relative to number of events.

A cautionary tale...

Long-acting Beta-Agonists with and without Inhaled Corticosteroids

Shelley R. Salpeter, MD, FACP,[a,b] Andrew J. Wall, MD,[a,b] Nicholas S. Buckley[c]

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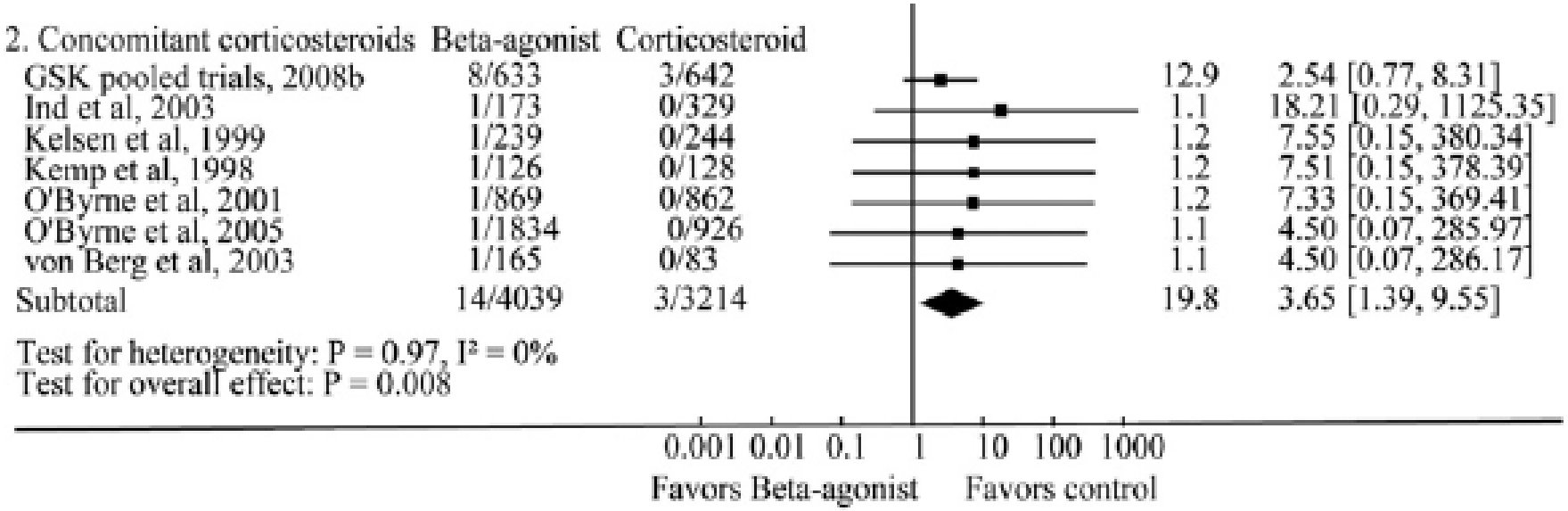
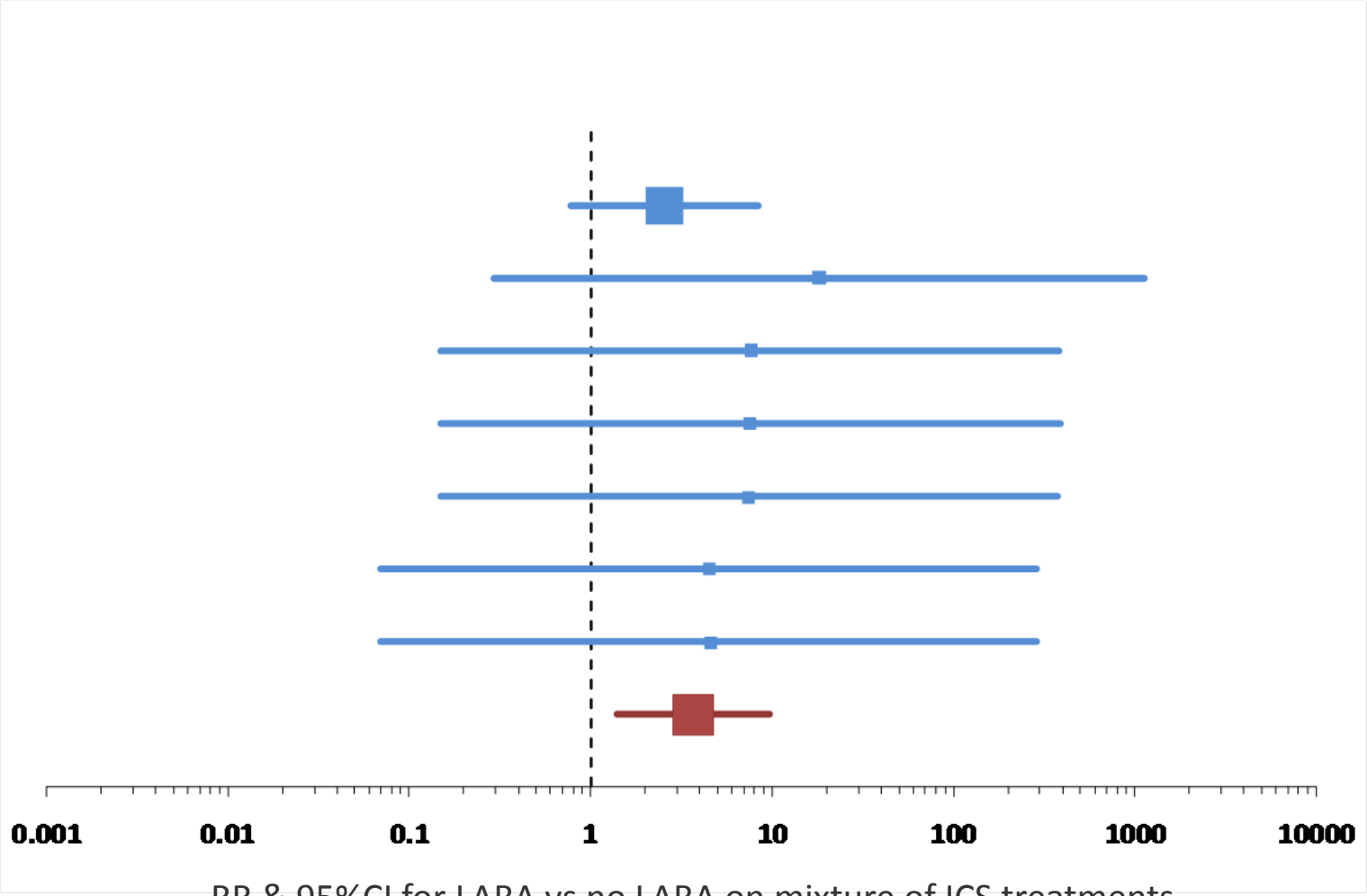


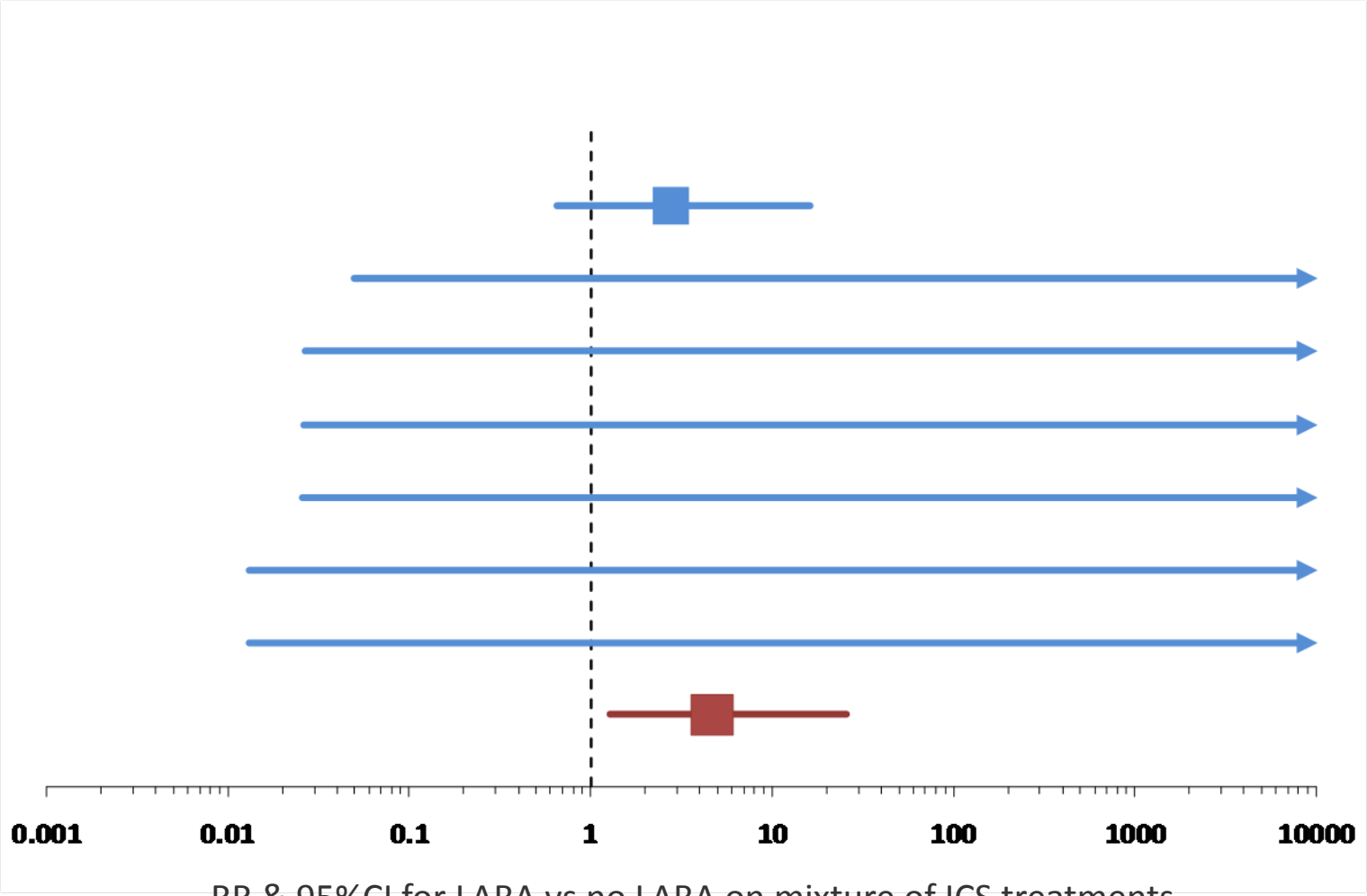
Published Online, February 2010.

Peto odds ratios as reported in the article



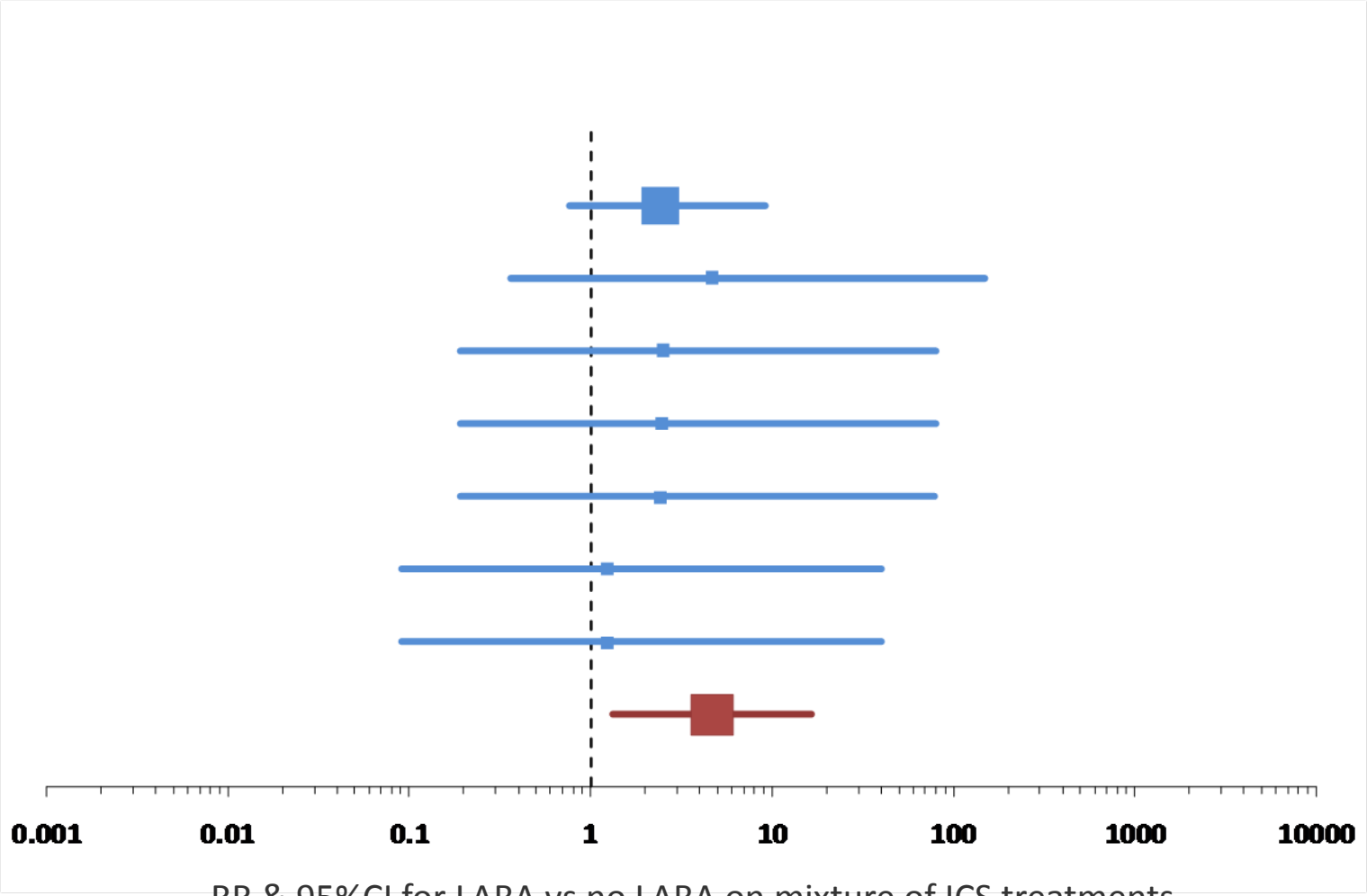
RR & 95%CI for LABA vs no LABA on mixture of ICS treatments

Exact analysis



RR & 95%CI for LABA vs no LABA on mixture of ICS treatments

M-H overall analysis with Bayes CIs for individual trials



RR & 95%CI for LABA vs no LABA on mixture of ICS treatments

Some issues...

- Excludes 83 trials with no events.
- Excludes 70 trials with a duration of less than 3 months.
- No process for adjudicating events.
- Odds ratio via the Peto method and addition of 0.5 to all cells where there was only one event.
- Mixture of background ICS of unknown dose, ICS in free combination with LABA and ICS in fixed combination with LABA.
- Only one trial compared ICS+LABA vs same dose of ICS.

Summary

- Increasingly regulators are asking Sponsors for the evaluation of all available clinical data in relation to the occurrence of some AE of concern.
- Often this is often triggered on just a handful of events, or some small unexpected imbalance or ‘signal’ in a large trial.
- Benefits in a standardised approach that is seemingly simple, statistically consistent and clinically meaningful approach versus the evaluation, presentation and aggregation of rare AE data across trials.
- Caution! Meta-analyses are complex and open to bias and abuse. Experienced statistical input and guidance is vital if damaging errors in interpretations and critical omissions of data are to be avoided.

Thank you.

Any questions?