Confronto tra studi osservazionali e trials nella Sclerosi Multipla

Graziella Filippini

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EDITORIAL

Neurology 2007

Is it time to use observational data to estimate treatment effectiveness in multiple sclerosis?

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Neurology® 2007;69:1478–1479

There is growing interest in the use of observational data to estimate treatment effects in chronic diseases such as multiple sclerosis (MS). While randomized, controlled trials (RCTs) have long been viewed as the gold standard for estimating treatment effects, there are instances in which they are unethical or impractical.[1] Even if an RCT is feasible, interest often focuses on estimating treatment effects in real-world settings, outside the tightly controlled confines of an RCT. Observational studies may be especially valuable for answering long-term questions in MS such as the long-term impact of currently available disease modifying drugs (DMDs) in preventing unremitting disability progression.[2] Open-label extensions of RCTs[3,4] also tried to assess this issue but

The popular belief that only RCTs produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and education of health care professionals. We should celebrate an enhanced quality of observational studies and the opportunity it provides for a less expensive evaluation of therapies in clinical medicine. It is time to move toward scientific investigations of the appropriate place for observational studies in evidence-based medicine. This article by Brown et

Observational studies - Cons

Provide no useful means of assessing the value of a therapy. *Doll R. Ann N Y Acad Sci 1994*

Should only be undertaken when RCTs are infeasible or unethical. *Deeks JJ et al. Health Technology Assessment 2003*

Selection bias, unclear exclusion, treatment and outcome measures not standardised, unblindness, data quality

Observational studies - Pro

A role in research into the benefits and harms of interventions

More suitable to detect rare or late adverse effects of treatments

More likely to provide an indication of what is achieved in daily medical practice (gen)

RCTs - cannot answer all important questions about a given intervention.

von Elm et al. STROBE. BMJ 2007

Italy

New Natural History of Interferon-β–Treated Relapsing Multiple Sclerosis

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Objective: To investigate the impact of interferon-beta (IFNβ) on disease progression in relapsing-remitting multiple sclerosis patients.

Methods: A cohort of 1,504 relapsing-remitting multiple sclerosis (1,103 IFNβ–treated and 401 untreated) patients was followed for up to 7 years. Cox proportional hazards regression adjusted for propensity score inverse weighting was used to assess the differences between the two groups for three different clinical end points: secondary progression (SP) and irreversible Expanded Disability Status Scale (EDSS) scores 4 and 6. Times from first visit and from date of birth were used as survival time variables.

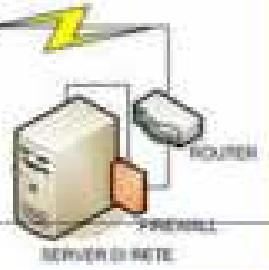
Results: The IFNβ–treated group showed a highly significant reduction in the incidence of SP (hazard ratio [HR], 0.38, 95% confidence interval [CI], 0.24–0.58 for time from 1st visit; HR, 0.36, 95% CI, 0.23–0.56 for time from date of birth; $p < 0.0001$), EDSS score of 4 (HR, 0.70, 95% CI, 0.53–0.94 for time from first visit; HR, 0.69, 95% CI, 0.52–0.93 for time from date of birth; $p < 0.02$), and EDSS score of 6 (HR, 0.60, 95% CI, 0.38–0.95 for time from first visit; HR, 0.54, 95% CI, 0.34–0.86 for time from date of birth; $p \leq 0.03$) when compared with untreated patients. SP and EDSS scores of 4 and 6 were reached with significant delays estimated by times from first visit (3.8, 1.7, and 2.2 years) and from date of birth (8.7, 4.6, and 11.7 years) in favor of treated patients. Sensitivity analysis confirmed findings.

Interpretation: IFN-β slows progression in relapsing-remitting multiple sclerosis patients.

Annals Neurology 2007

The Italian multiple sclerosis database network

Consorzio "Mario Negri Sud"
S. Maria Imbaro (CH)



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Analysis

MS CENTERS IN ITALY

Nova Scotia Canada

How effective are disease-modifying drugs in delaying progression in relapsing-onset MS?

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ABSTRACT

Objective: Our objective was to estimate the effectiveness of disease-modifying drugs (DMDs) in delaying multiple sclerosis (MS) disability progression in relapsing-onset (R-onset) definite MS patients under "real-world" conditions.

Methods: Treatment effect size, for DMDs as a class, was estimated in absolute terms and relative to MS natural history. A basic model estimated annual Expanded Disability Status Scale (EDSS) change before and after treatment. An expanded model estimated annual EDSS change in pretreatment years, treatment years on first drug, treatment years after drugs were switched, and in years after treatment stopped. Models were populated with 1980 through 2004 clinical data, including 1988 through 2004 data for all Nova Scotians treated with DMDs. Estimates were made for relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and R-onset groups.

Conclusions: Our estimates of disease-modifying drug (DMD) relative treatment effect size, in the context of "real-world" clinical practice, are similar to DMD treatment efficacy estimates in pivotal trials, though our findings attained statistical significance. DMDs, as a class, are effective in delaying Expanded Disability Status Scale progression in patients with relapsing-onset definite multiple sclerosis (MS) (90%), although effectiveness is much better for relapsing-remitting MS than for secondary progressive MS groups. *Neurology*® 2007;69:1498-1507

The Dalhousie MS database - 25 years of clinical data, up to 6 years of treatment data.

Clinical characteristics of responders to interferon therapy for relapsing MS

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France

Abstract—*Objective:* To determine the proportion of patients with multiple sclerosis (MS) who respond to interferon-β (IFNB) therapy and assess whether clinical characteristics differ in IFNB responders vs nonresponders. *Methods:* Data on all patients who received IFNB who were entered in the prospective European Database for Multiple Sclerosis (EDMUS) database in Lyon as of March 31, 2001, were reviewed. Responders were defined as having a lower relapse rate on IFNB compared with the year or 2 years prior to IFNB therapy. *Results:* Two hundred sixty-two patients with relapsing MS received at least 6 months of IFNB: 200 relapsing remitting (RR) and 62 relapsing secondary progressive (SP). One-third of patients experienced a higher or identical annual relapse rate while on IFNB treatment. Compared with nonresponders, responders were older and had longer disease duration at the time IFNB was initiated. RRMS responders also had a higher relapse rate during the year prior to IFNB therapy and SPMS responders had a higher Disability Status Scale score at initiation of IFNB. *Conclusion:* Clinical profiles of patients with relapsing MS who respond to IFNB may differ from those who do not with a more inflammatory and less neurodegenerative disease at the time IFNB is initiated.

Neurology 2003

3,177 MS patients in Lyon's EDMUS database

The Multiple Sclerosis Risk Sharing Scheme Monitoring Study early results and lessons for the future

UK

Pickin et al. BMC Neurology 2009

Abstract

Background: Risk sharing schemes represent an innovative and important approach to the problems of rationing and achieving cost-effectiveness in high cost or controversial health interventions. This study aimed to assess the feasibility of risk sharing schemes, looking at long term clinical outcomes, to determine the price at which high cost treatments would be acceptable to the NHS.

Methods: This case study of the first NHS risk sharing scheme, a long term prospective cohort study of beta interferon and glatiramer acetate in multiple sclerosis (MS) patients in 71 specialist MS centres in UK NHS hospitals, recruited adults with relapsing forms of MS, meeting Association of British Neurologists (ABN) criteria for disease modifying therapy. Outcome measures were: success of recruitment and follow up over the first three years, analysis of baseline and initial follow up data and the prospect of estimating the long term cost-effectiveness of these treatments.

Results: Centres consented 5560 patients. Of the 4240 patients who had been in the study for a least one year, annual review data were available for 3730 (88.0%). Of the patients who had been in the study for at least two years and three years, subsequent annual review data were available for 2055 (78.5%) and 265 (71.8%) patients respectively. Baseline characteristics and a small but statistically significant progression of disease were similar to those reported in previous pivotal studies.

Conclusion: Successful recruitment, follow up and early data analysis suggest that risk sharing schemes should be able to deliver their objectives. However, important issues of analysis, and political and commercial conflicts of interest still need to be addressed.

Problems with UK government's risk sharing scheme for assessing drugs for multiple sclerosis

Cathie L M Sudlow, Carl E Counsell

BMJ 2005

Summary points

NICE has announced that neither interferon beta nor glatiramer can be recommended for multiple sclerosis in the NHS

The Department of Health plans to make these drugs available through a risk sharing scheme that is scientifically unsound and impractical

Randomised trials suggest that azathioprine (which is 20 times cheaper) may be just as effective

The long term effectiveness of these drugs is unknown

Government money would be better spent on a long term randomised trial comparing interferon beta or glatiramer with azathioprine and no treatment

Storia Naturale SM - Key Points

- decorso 30-40 anni

- disabilità motoria e cognitiva – esito a maggior impatto clinico, sociale ed economico

- determinante maggiore – decorso progressivo

- frequenza ricadute – non correla con la disabilità a lungo termine

Nat Hist 1-9 -Weinshenker et ,Cottrell et Kremenchutzky et, Ebers et 1989-2007 - 1044 pazienti, followup medio 25 anni - reanalisi 25,000 pazienti 30 anni

Storia naturale della SM - tempi mediani alla disabilità

Relapsing Remitting	Primary Progressive
EDSS 6 - 15 anni	EDSS 6 - 8 anni
EDSS 7 - 20 anni	EDSS 7 - 12 anni
EDSS 8 - 25 anni	EDSS 8 - 15 anni

DMD *vs* placebo in Cochrane SRs

Intervention	*Type of MS*	*Outcome*	*Follow up time*	*No of patients (No of trials)*	*Control group risk (Range)*	*Protocol analysis*		*Sensitivity analysis*
						RR (95% CI)	*Risk difference (95% CI)*	*RR (95% CI)*
INTERFERONS β (5 RCTs)	RR	recurrence of relapses	1 year	582 (3)	68% (57-78%)	0.73 (0.55-0.97)	-23% (-8 to -39%)	-
			2 years	919 (3)	69% (45-84%)	0.80 (0.73-0.88)	-14% (-8 to -19%)	1.11 (0.73-1.68)
		progression of disability	2 years	919 (3)	29% (20-36%)	0.69 (0.55-0.87)	-9% (-3 to -14%)	1.31 (0.60-2.89)
COPOLIMERO (4 RCTs)	RR CP	recurrence of relapses	1 year	289 (2)	54% (51-68%)	0.64 (0.31-1.34)	-	
			2 years	301 (2)	72% (68-73%)	0.87 (0.74-1.02)	-	
		progression of disability	2 years	407 (3)	27% (25-44%)	0.77 (0.51-1.14)	-	

DMD *vs* placebo in Cochrane SRs

Intervention	*Type of MS*	*Outcome*	*Follow up time*	*No of patients (No of trials)*	*Control group risk (Range)*	*Protocol analysis*		*Sensitivity analysis*
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RCTs - DMD vs placebo
Key Points

- Max 2-anni follow-up

- Esiti primari - Misure surrogate, a breve termine, non validate per la disabilità irreversibile
  frequenza ricadute, score disabilità (3/6 mesi), MRI

- Perdite al follow-up (anche >40%)

- Non cecità

- Conflitto di interessi

Key Points

- Ostacoli formidabili per conclusioni valide

  riduzione errore misura, controllo non cecità, estendere la durata dei trial mantenendo intatta la partecipazione

- Le decisioni cliniche nella SM appoggiano su trials di breve durata & misure di outcome suscettibili a bias & errori di misura - sono esterni ad una base di evidenza

RCTs - DMD confronti diretti

Schwid et al. Avonex high dose and frequency. Arch Neurol 2005	32 settimane 607 partecipanti
Panitch et al. Rebif vs Avonex. Neurology 2002	24-48 settimane 677 partecipanti
Mikol et al. Rebif vs Glatiramer. Lancet Neurology 2008	96 settimane 764 partecipanti

Nessun vantaggio di un farmaco rispetto all'altro,
nè per tipo nè per dosaggio.
I nuovi trials molto meno informativi dei trial storici IFNB

Considerazioni sui nuovi trials

- Tasso di ricadute annuo < 50% rispetto ai trials degli anni ’90
- Anticipazione diagnostica in base a nuovi criteri (McDonald)
- Incremento dimensioni studio per compensare la riduzione di potenza (bassa numerosità eventi)
- Sample size ↑ Durata follow-up ↓

Studi osservazionali - Key Points

Problemi precedenti e nuovi:

- Bias selezione, gruppi non confrontabili *(trattati meno gravi, controlli eventi avversi da IFN, cont. storici*)
- Outcome surrogati a breve termine (def. disabilità)
- Non cecità
- Strategie di aggiustamento non garantiscono per variabili prognostiche ignote o non considerate (*Deeks JJ et al. Health Technology Assessment 2003*)

Studi osservazionali - Key Points

Problemi precedenti e nuovi:

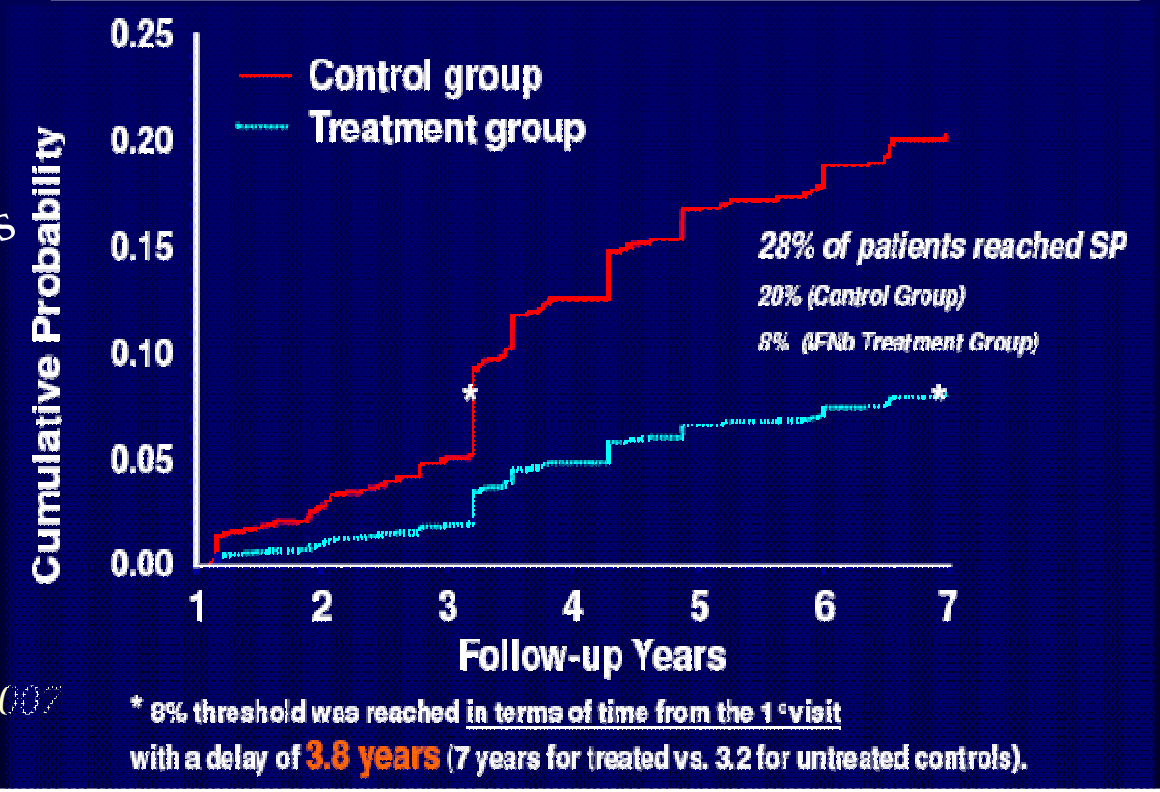
- Deviazioni, esclusi, persi, non riportati
- No analisi per intenzione al trattamento
- Frequenza, dimensione, direzione dei bias non interpretabile per mancanza di informazioni
- Conflitto di interessi

IFNB *vs* NT. Studi osservazionali

Italy

Variable	IFNβ	Untreated	All	p-value
N	1103	401	1504	
Age onset	26.5±8.4	29.9±9.9	27.4±9.0	<0.0001
Duration	**6.9±6.0**	**4.1±6.0**	6.2±6.2	<0.0001
EDSS	2.3±0.9	1.5±0.8	2.1±1.0	<0.0001
N bouts last yr	1.4±0.8	0.6±0.7	1.2±0.9	<0.0001

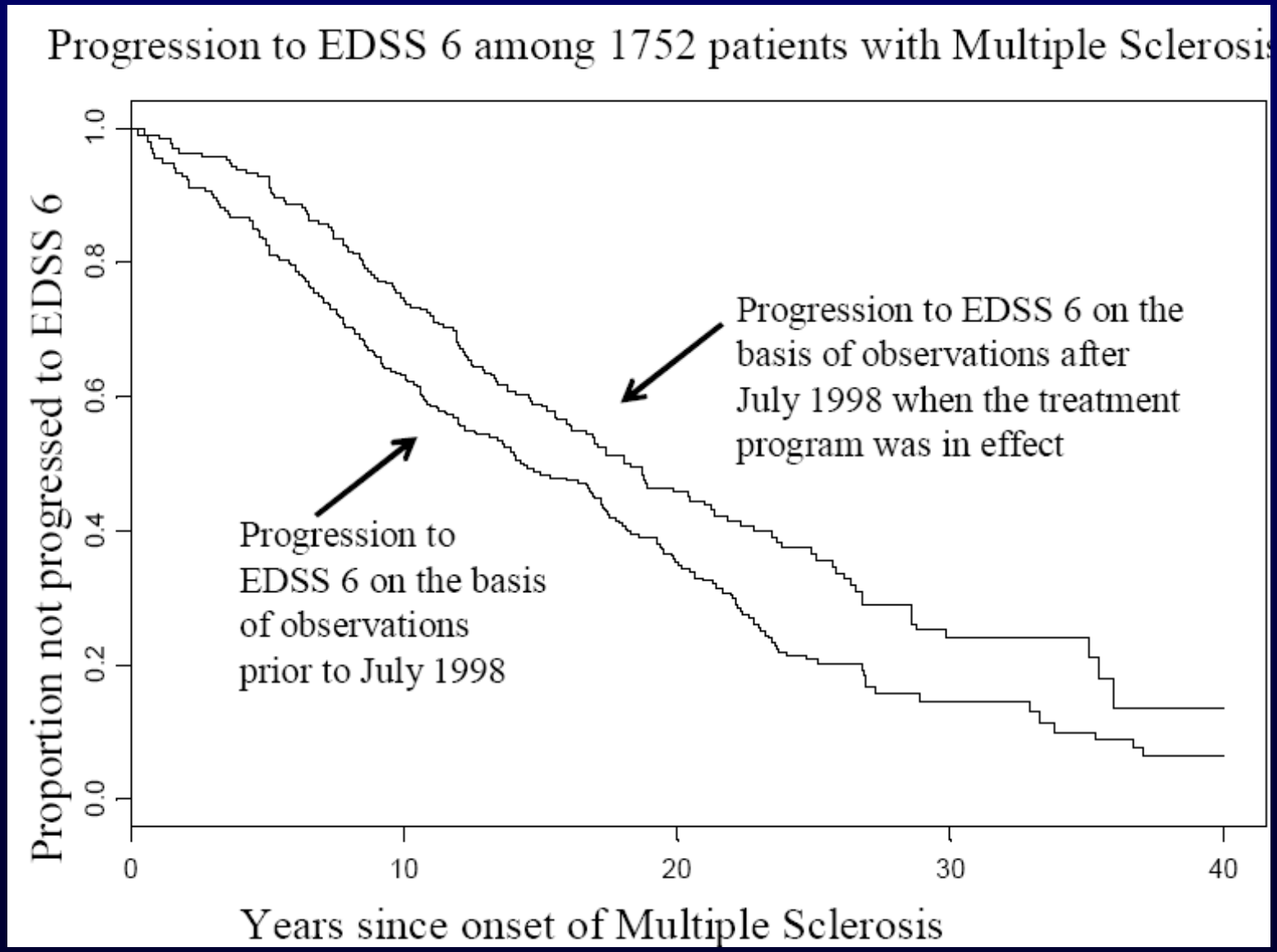
median fwup 5.7 yrs



Trojano, Ann Neurol 2007

Nova Scotia
Canada

DMD *vs* NT. Studi osservazionali



Brown et al. Neurology 2007

IFNB *vs* NT. Studi osservazionali

France - EDMUS

200 RRMS and 62 SPMS

- 58% responders - lower relapse rate, no change on DSS, and no progression to SPMS while on IFNB
- Responders: older, longer disease duration, higher relapse rate during the year prior to IFNB
- SPMS responders: higher DSS score at initiation of IFNB

Waubant et al. Neurology 2003

DMD comparison. Studi osservazionali

308 RRMS – follow-up 2 anni

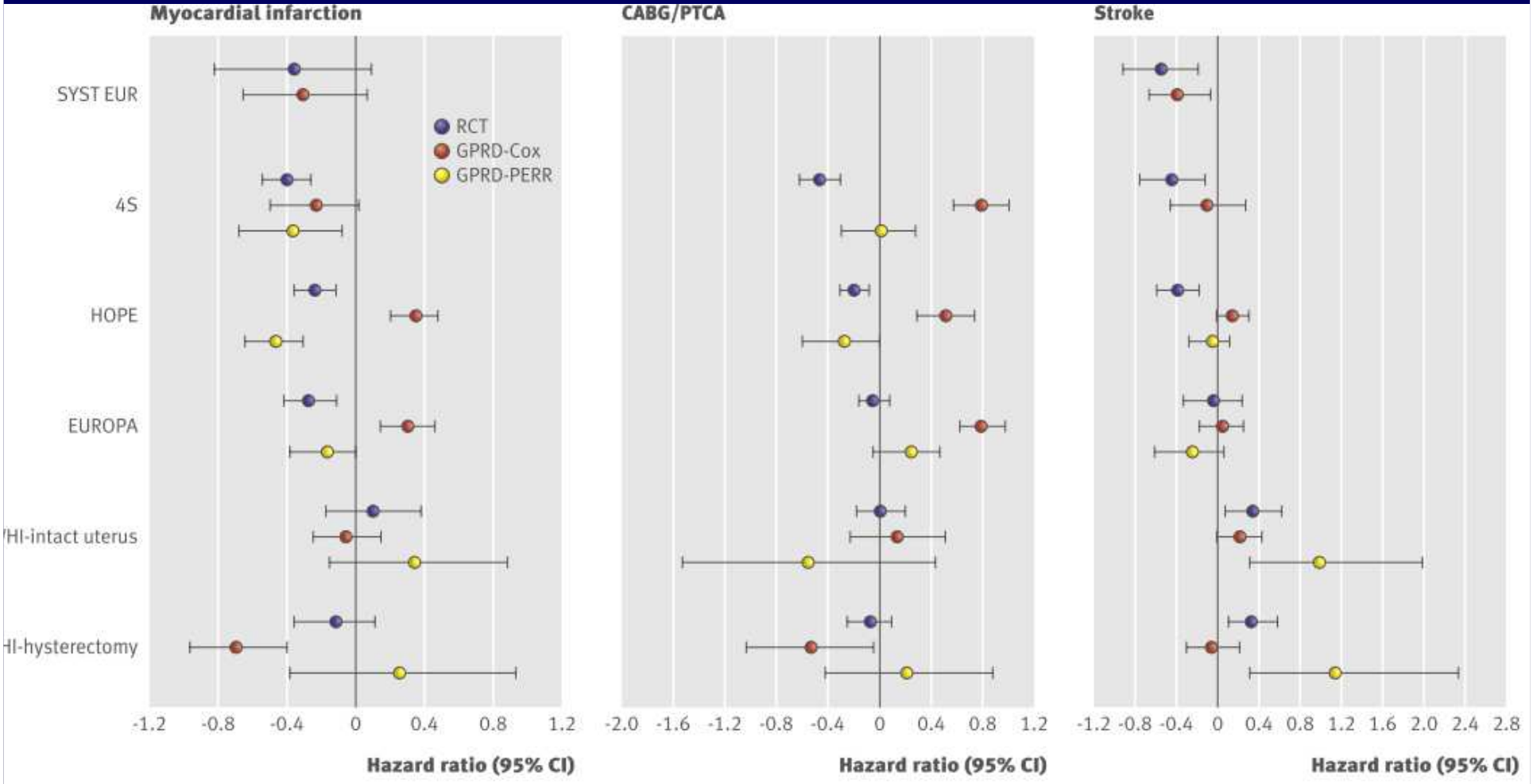
Outcome	IFNß1b	IFNß1a sc	IFNß1a im	Glatiramer acetate	P-value
Annualised Relapse Rate	0.69	0.66	0.8	0.36	**<0.001**
% Relapse-free	45.5	45.8	35.4	58.2	0.22
DC treatment after 6 mos	22.9	31.2	32.9	8.9	**<0.001**
% Progression-free	71.7	73.3	74.5	87.5	0.13

Haas et al. *European Journal of Neurology* 2005

RCTs & Osservazionali -proposte

- Necessari entrambi
- Rigore, Qualità (RCTs & osservazionali)
- Modelli di analisi (osservazionali)
- Trasparenza & Indipendenza
- Reporting: CONSORT, STROBE

Use of primary care electronic medical record database in drug efficacy research on cardiovascular outcomes: comparison of database and randomised controlled trial findings



Tannen et al. BMJ 2009;338:b81

The underlying hypothesis of the PERR analytical technique is that a comparison between the event rate for a specific outcome in a cohort's exposed and unexposed patients before entry into the study should reflect the effect of all confounders on that specific outcome independent of the effect of treatment.