S.I.M.G. - Società Italiana di Medicina Generale

Confondimento da indicazione ed *immeasurable time-bias*: alcuni esempi pratici

Francesco Lapi, PharmD, PhD

Health Search, Società Italiana di Medicina Generale

Confondimento da indicazione (1)

Definizione:

"confounding by indication may arise when a drug treatment serves as a marker for a clinical characteristic or medical condition that triggers the use of the treatment and that, at the same time, increases the risk of the outcome under study"

Psaty BM et al. JAGS 47: 749-754, 1999.

Metodi per “minimizzare” il confondimento da indicazione

- Restrizione ad una coorte con caratteristiche simili/scelta della reference category
- Stratificazione e stime pooled
- Disegno case-crossover
- Propensity Score o High Dimensional Propensity Score
- Modelli Marginali Strutturali
- Variabili strumentali
- External adjustement

Metodi per “minimizzare” il confondimento da indicazione

- **Restrizione ad una coorte con caratteristiche simili/scelta della reference category**
- Stratificazione e stime pooled
- Disegno case-crossover
- Variabili strumentali
- Propensity Score o High dimensional Propensity Score
- Modelli Marginali Strutturali
- External adjustement

Confondimento da indicazione (4) - Esempio

Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study

Francesco Lapi *pharmacoepidemiology fellow*[1 2 3], Laurent Azoulay *assistant professor*[1 4], Hui Yin *statistician*[1], Sharon J Nessim *assistant professor and nephrologist specialist*[5], Samy Suissa *professor and director*[1 2]

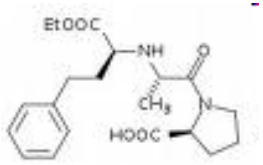
[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Côte Sainte-Catherine Montreal, Quebec, Canada, H3T 1E2; [2]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada, H3A 1A2; [3]Department of Preclinical and Clinical Pharmacology, University of Florence, 50139 Florence, Italy; [4]Department of Oncology, McGill University, Montreal, Quebec, Canada, H3G 1A4; [5]Department of Medicine, Division of Nephrology, Jewish General Hospital, Montreal, Quebec, Canada, H3T 1E2

BMJ 2013;346:e8525

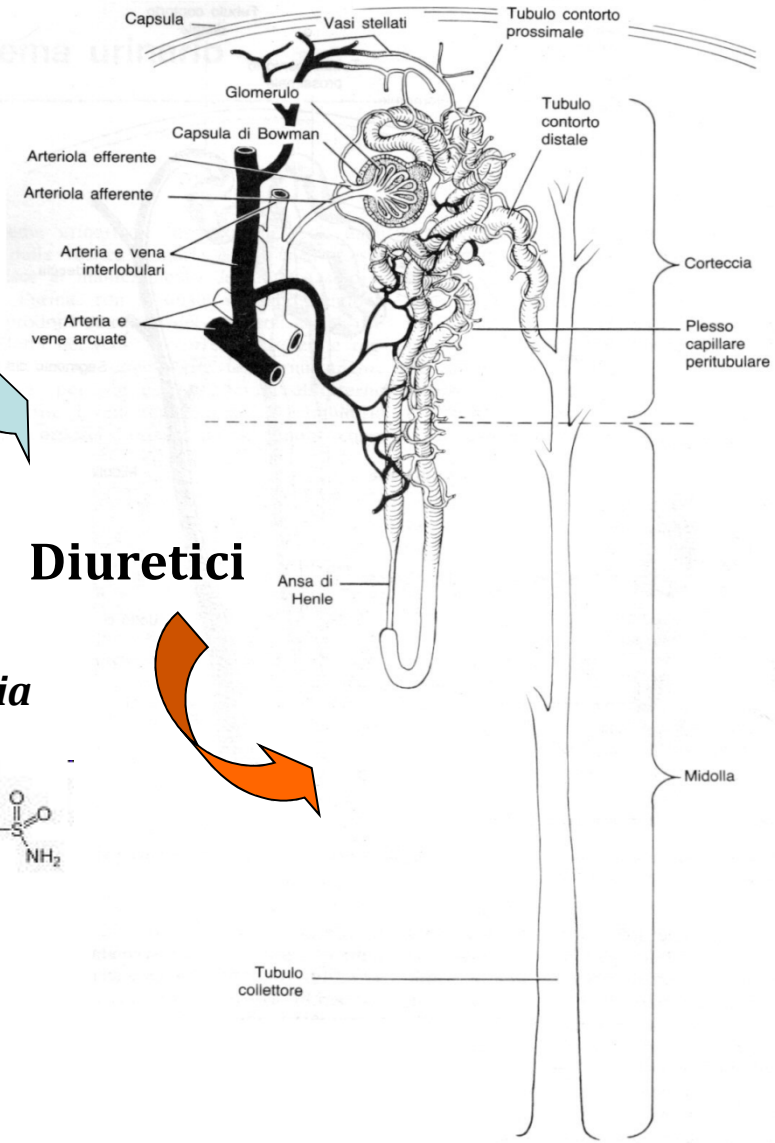
Razionale biologico

ACEIs or ARBs

Vasodilatazione efferente

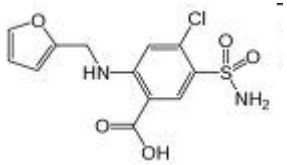


enalapril



Diuretici

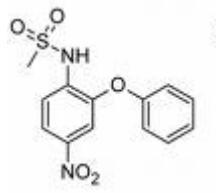
Ipovolemia



furosemide

NSAIDs (incl. COX inib.)

Vasocostrizione afferente



nimesulide

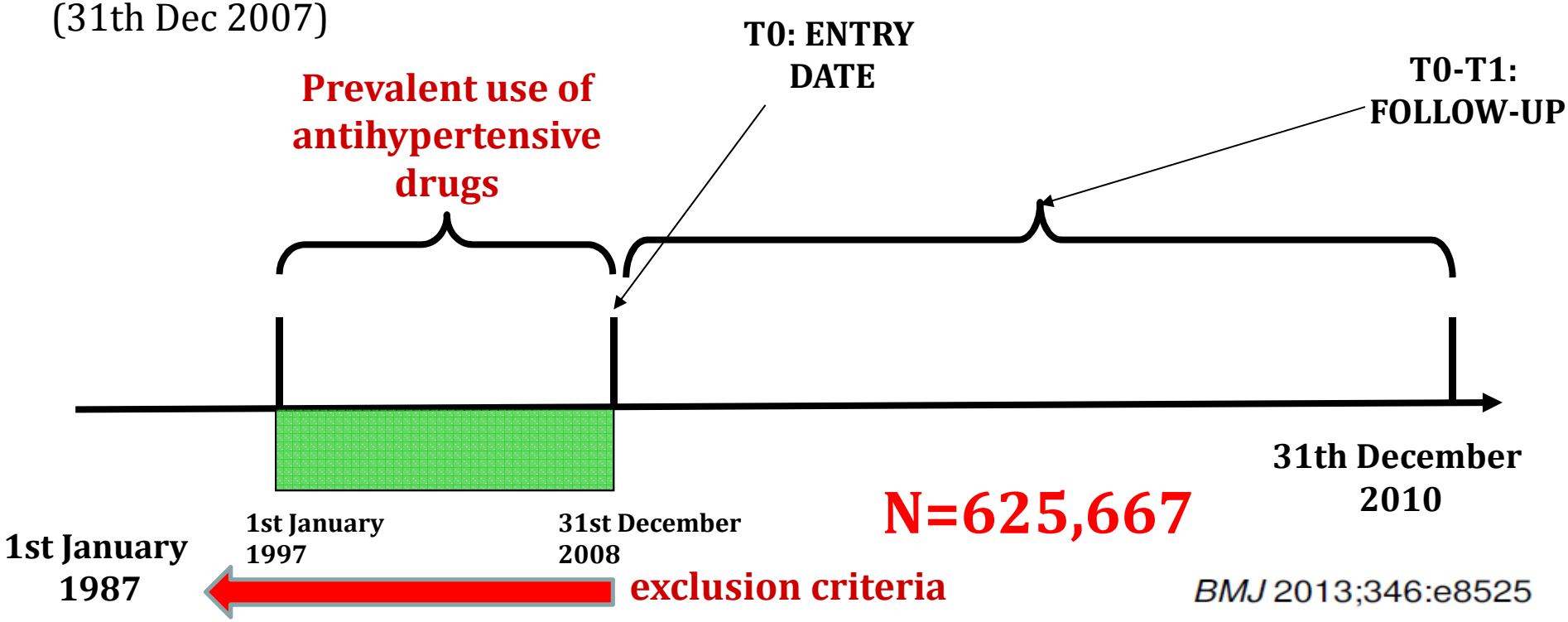
BMJ 2013;346:e8525

Metodi (1) - Definizione della coorte

Exclusion criteria: Read code of cancer, chronic or acute kidney failure (including dialysis-related procedures; in both HES and GPRD data), hepatitis, systemic connective tissue disease, rheumatoid arthritis, crush injury, HIV infection, drug abuse

T0 (ENTRY DATE): prescription of antihypertensive drugs

T1 (EXIT DATE): ICD10 (primary diagnosis) related to AKI (index date), one of the exclusion criteria (incl. AKI as secondary diagnosis in HES data), death, data availability (31th Dec 2007)



BMJ 2013;346:e8525

Risultati (1)

Table 2| **Rate ratio of acute kidney injury associated with exposure to current double or triple therapy combination. Values are numbers (percentages) unless stated otherwise**

Current use*	Cases (n=2215)	Controls (n=21 993)	Rate ratio (95% CI)	
			Crude	Adjusted†
Diuretics only	209 (9.4)	2632 (12.0)	Reference	Reference
Diuretics plus NSAIDs	156 (7.0)	1739 (7.9)	1.16 (0.93 to 1.44)	1.02 (0.81 to 1.28)
ACE inhibitors or angiotensin receptor blockers only	148 (6.7)	1889 (8.6)	Reference	Reference
ACE inhibitors or angiotensin receptor blockers plus NSAIDs	138 (6.2)	1907 (8.7)	0.96 (0.75 to 1.22)	0.89 (0.69 to 1.15)
Diuretics plus ACE inhibitors or angiotensin receptor blockers	414 (18.7)	2432 (11.1)	Reference	Reference
Diuretics plus ACE inhibitors or angiotensin receptor blockers plus NSAIDs	544 (24.6)	2424 (11.0)	1.34 (1.17 to 1.54)	1.31 (1.12 to 1.53)

ACE=angiotensin converting enzyme; NSAID=non-steroidal anti-inflammatory drug.

*Within 90 days before index date; current users of other antihypertensive drugs and past users (>90 days before index date) of double and triple therapy combinations are not shown but were considered in regression model.

†Adjusted for covariates listed in table 1.

BMJ 2013;346:e8525

Risultati (2) – Stratificazione per osteoartrosi

Table G. Rate ratio of acute kidney injury associated with exposure to current double or triple therapy combination stratifying by osteoarthritis diagnosis.

Current Use*	Cases n=2215	Controls n=21 993	RR (95% CI) crude	RR (95% CI) adjusted†
Without osteoarthritis:				
diuretics only	165 (9.4)	2175 (12.1)	Reference	Reference
diuretics plus NSAIDs	122 (6.9)	1361 (7.6)	1.21 (0.94 to 1.55)	1.03 (0.79 to 1.35)
ACEIs or ARBs only	117 (6.6)	1618 (9.0)	Reference	Reference
ACEIs or ARBs plus NSAIDs	115 (6.5)	1564 (8.7)	1.03 (0.78 to 1.35)	0.99 (0.74 to 1.33)
diuretics plus ACEIs or ARBs	327 (18.5)	1969 (11.0)	Reference	Reference
diuretics plus ACEIs or ARBs plus NSAIDs	418 (23.7)	1920 (10.7)	1.39 (1.18 to 1.64)	1.38 (1.15 to 1.65)
With osteoarthritis:				
diuretics only	44 (9.8)	457 (11.2)	Reference	Reference
diuretics plus NSAIDs	34 (7.6)	378 (9.3)	0.76 (0.43 to 1.36)	0.69 (0.36 to 1.33)
ACEIs or ARBs only	31 (6.9)	271 (6.7)	Reference	Reference
ACEIs or ARBs plus NSAIDs	23 (5.1)	343 (8.4)	0.64 (0.32 to 1.26)	0.61 (0.28 to 1.31)
diuretics plus ACEIs or ARBs	87 (19.3)	463 (11.4)	Reference	Reference
diuretics plus ACEIs or ARBs plus NSAIDs	126 (28.0)	504 (12.4)	1.19 (0.79 to 1.80)	1.30 (0.81 to 2.09)

Values are reported as n (%); RR=rate ratio; CI=confidence interval
*Within 90 days before the index date; current users of other antihypertensive drugs and past users (more than 90 days before the index date) of double and triple therapy combinations are not displayed in the table, but were considered in the regression model
†Adjusted for the covariates listed in Table 1

BMJ 2013;346:e8525

Confondimento da indicazione (5) - Esempio

Original Investigation

Androgen Deprivation Therapy and Risk of Acute Kidney Injury in Patients With Prostate Cancer

Francesco Lapi, PharmD, PhD; Laurent Azoulay, PhD; M. Tamim Niazi, MD; Hui Yin, MSc; Serge Benayoun, MD, MSc; Samy Suissa, PhD

JAMA July 17, 2013 Volume 310, Number 3

Risultati (1)

Table 3. Risk of Acute Kidney Injury Associated With Androgen Deprivation Therapy According to Timing of Use

	Exposure to Androgen Deprivation Therapy		
	Never	Current (≤90 d of Index Date)	Past (≥91 d of Index Date)
No. (%)			
Cases (n = 232)	40 (17.2)	168 (72.4)	24 (10.3)
Controls (n = 2721)	842 (30.9)	1420 (52.2)	459 (16.9)
OR (95% CI)			
Crude	1 [Reference]	2.66 (1.83-3.85)	1.12 (0.66-1.93)
Adjusted[a]	1 [Reference]	2.48 (1.61-3.82)	1.25 (0.68-2.29)

Abbreviation: OR, odds ratio.

[a] Adjusted for excessive alcohol use, smoking status, obesity, prostate-specific antigen, hypertension, coronary artery disease, diabetes, rhythm disorders, congestive heart failure, ischemic stroke, number of hospitalizations, metastasis, radiation therapy, prostatectomy, chemotherapy, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers, other antihypertensives (including diuretics), antibiotics, paracetamol/acetaminophen, aspirin, statins, corticosteroids, antiarrhythmics, other nonsteroidal anti-inflammatory drugs, anticoagulants, selective serotonin reuptake inhibitors, digoxin, clopidogrel, immunosuppressive agents, and antipsychotics.

JAMA July 17, 2013 Volume 310, Number 3

Risultati (2)

Table 4. Risk of Acute Kidney Injury Associated With Androgen Deprivation Therapy According to Type of Therapy

Exposure to Androgen Deprivation Therapy	No. (%)		OR (95% CI)	
	Cases (n = 232)	Controls (n = 2721)	Crude	Adjusted[a]
Never	40 (17.2)	842 (30.9)	1 [Reference]	1 [Reference]
Current[b]				
Combined androgen blockade	43 (18.5)	208 (7.6)	4.51 (2.80-7.27)	4.50 (2.61-7.78)
Estrogen only	5 (2.2)	15 (0.6)	7.03 (2.35-21.04)	4.00 (1.06-15.03)
Other combination therapies	19 (8.2)	69 (2.5)	5.56 (2.97-10.38)	4.04 (1.88-8.69)
Oral antiandrogens only	10 (4.3)	112 (4.1)	2.03 (0.97-4.23)	2.18 (0.95-5.01)
GnRH agonists only	85 (36.6)	949 (34.9)	1.99 (1.32-3.00)	1.93 (1.20-3.10)
Bilateral orchiectomy	6 (2.6)	67 (2.5)	1.59 (0.61-4.11)	1.84 (0.64-5.28)

Abbreviations: GnRH, gonadotropin-releasing hormone; OR, odds ratio.

[a] Adjusted for excessive alcohol use, smoking status, obesity, prostate-specific antigen, hypertension, coronary artery disease, diabetes, rhythm disorders, congestive heart failure, ischemic stroke, number of hospitalizations, metastasis, radiation therapy, prostatectomy, chemotherapy, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers, other antihypertensives (including diuretics), antibiotics, paracetamol/acetaminophen, aspirin, statins, corticosteroids, antiarrhythmics, other nonsteroidal anti-inflammatory drugs, anticoagulants, selective serotonin reuptake inhibitors, digoxin, clopidogrel, immunosuppressive agents, antipsychotics.

[b] *P* value for interaction across the different ADT exposure groups was .001.

JAMA July 17, 2013 Volume 310, Number 3

Analisi di sensibilità per “minimizzare” il confondimento da indicazione

- constrasting tra “current users” e “past users”
- esclusione dei soggetti con elevati valori di creatinina al baseline; censoring a causa dell’insorgenza di metastasi, chemioterapia, per la durata massima di 2 anni (limitare l’impatto del disease progression)
- uso di falsification exposure (inibitori della 5alfa reduttasi)

Risultati (3) – Contrasting 'Current' vs. 'Past'/ulteriore restrizione della coorte

eTable 4. Risk of acute kidney injury associated with exposure to androgen deprivation therapy (reference category is the past use of ADT)

	Cases (n=232)	Controls (n=2721)	Crude RR (95% CI)	Adjusted RR (95% CI)[a]
Past use, No. (%)	24 (10.3)	459 (16.9)	1.00(reference)	1.00 (reference)
Current use, No. (%)	168 (72.4)	1420 (52.2)	2.36 (1.47, 3.81)	2.08 (1.22, 3.56)

Abbreviations: RR, rate ratio; CI, confidence interval

Current use: overlapping or within 90 days prior to the index date; Past use: exposure at any time between cohort entry and the 91 days before the index date

[a] adjusted for variables listed in Table 1

eTable 6. Risk of acute kidney injury associated with androgen deprivation therapy according to timing of use (excluding patients with abnormal creatinine values, followed for a maximum of two years, and additionally censoring on metastasis and chemotherapy)

Exposure to androgen deprivation therapy	Cases (n=28)	Controls (n=250)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Never use, No. (%)	6 (21.4)	80 (32.0)	1.00 (reference)	1.00 (Reference)
Current use, No. (%)	21 (75.0)	153 (61.2)	2.33 (0.75, 7.23)	4.54 (0.31-65.54)
Past use, No. (%)	1 (3.6)	17 (6.8)	1.32 (0.13, 13.39)	0.02 (0.00-11.17)

Abbreviations: OR, odds ratio; CI, confidence interval.

Current use: overlapping or within 90 days prior to the index date; Past use: exposure at any time between cohort entry and the 91 days before the index date

[a] Adjusted for excessive alcohol use, smoking status, obesity, prostate-specific antigen, hypertension, coronary artery disease, diabetes, rhythm disorders, congestive heart failure, ischemic stroke, number of hospitalizations, metastasis, radiation therapy, prostatectomy, chemotherapy, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, other antihypertensives (including diuretics), antibiotics, paracetamol, aspirin, statins, corticosteroids, antiarrhythmics, other non-steroidal anti-inflammatory drugs, anticoagulants, selective serotonin reuptake inhibitors, digoxin, clopidogrel, immunosuppressive agents, antipsychotics.

Risultati (4) – *Falsification exposure*

eTable7. Risk of acute kidney injury associated with 5-alpha reductase inhibitors according to timing of use

	Cases (n=232)	Controls (n=2721)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Never use, No. (%)	213 (91.8)	2502 (91.8)	1.00 (reference)	1.00 (Reference)
Current use, No. (%)	6 (2.6)	68 (2.5)	0.88 (0.36, 2.14)	0.62 (0.21-1.84)
Past use, No. (%)	13 (5.6)	151 (5.6)	1.09 (0.60, 1.98)	1.11 (0.57-2.19)

Abbreviations: OR, odds ratio; CI, confidence interval.

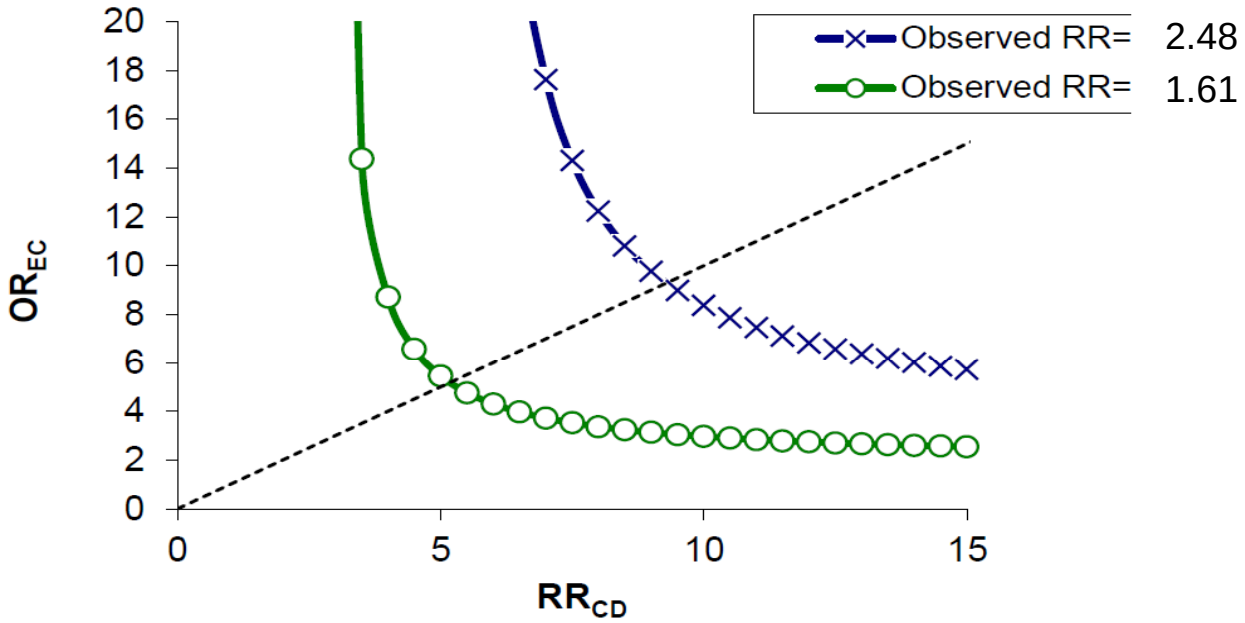
Current use: overlapping or within 90 days prior to the index date; Past use: exposure at any time between cohort entry and the 91 days before the index date

[a] Adjusted for excessive alcohol use, smoking status, obesity, prostate-specific antigen, hypertension, coronary artery disease, diabetes, rhythm disorders, congestive heart failure, ischemic stroke, number of hospitalizations, metastasis, radiation therapy, prostatectomy, chemotherapy, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, other antihypertensives (including diuretics), antibiotics, paracetamol, aspirin, statins, corticosteroids, antiarrhythmics, other non-steroidal anti-inflammatory drugs, anticoagulants, selective serotonin reuptake inhibitors, digoxin, clopidogrel, immunosuppressive agents, antipsychotics, and androgen deprivation therapy.

JAMA July 17, 2013 Volume 310, Number 3

Risultati (5) – *Effect size* del confondimento da indicazione

eFigure 1. Strength of an unmeasured confounder needed to explain a RR of 2.48



Blue line: observed Rate Ratio (RR); Green line: lower bound of the confidence intervals. OR_{EC}: odds ratio for the exposure-confounder association; RR_{CD}: relative risk for the confounder-disease association.

Assumptions: Based on an observed RR of 2.48 (i.e. current use (90 days prior to the index date) of androgen deprivation therapy (ADT) versus non-use in relation to acute kidney injury (AKI)) an exposure prevalence of 50% among controls (as representing the general population), and a confounder prevalence of 20%.

JAMA July 17, 2013 Volume 310, Number 3

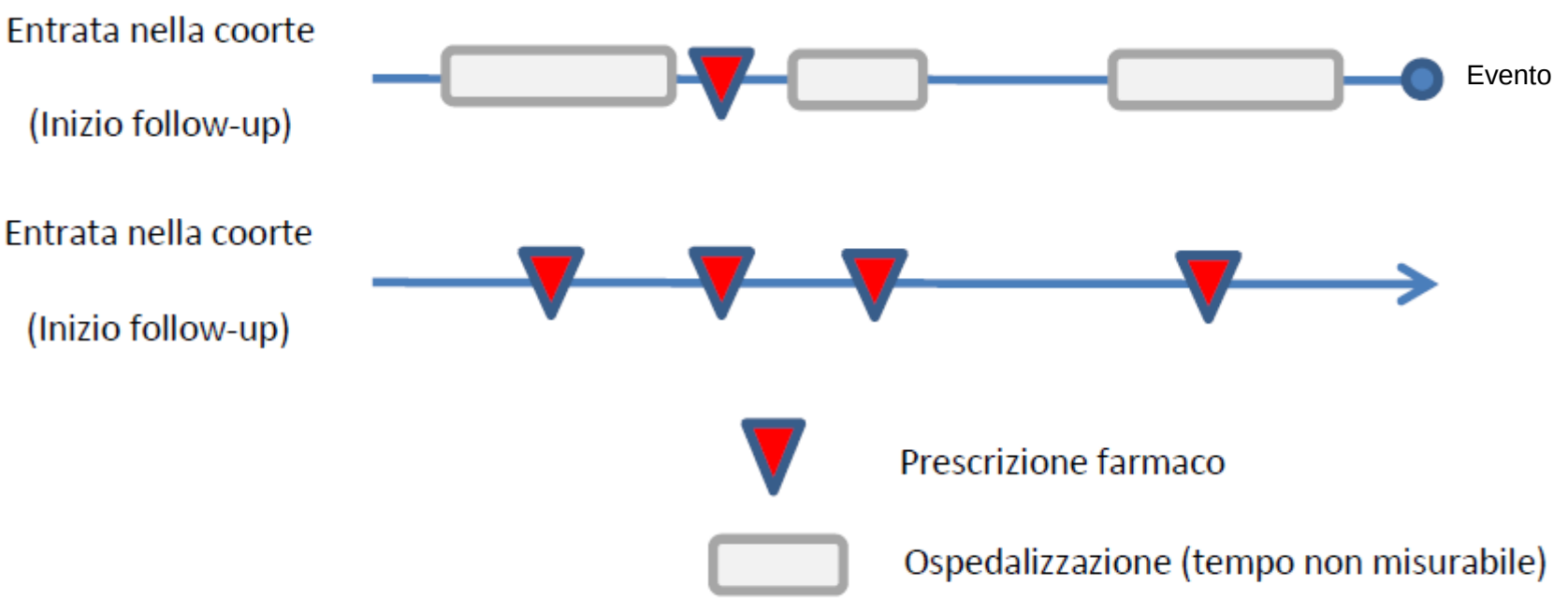
Immeasurable time-bias (1)

Definizione:

"Immeasurable time refers to a period of time during follow-up, for a cohort study, or prior to the index date, for a case-control study, during which a subject cannot be recognized as being exposed, albeit unknowingly to the investigator" (Suissa et al., 2008)

Am J Epidemiol 2008;168:329–335

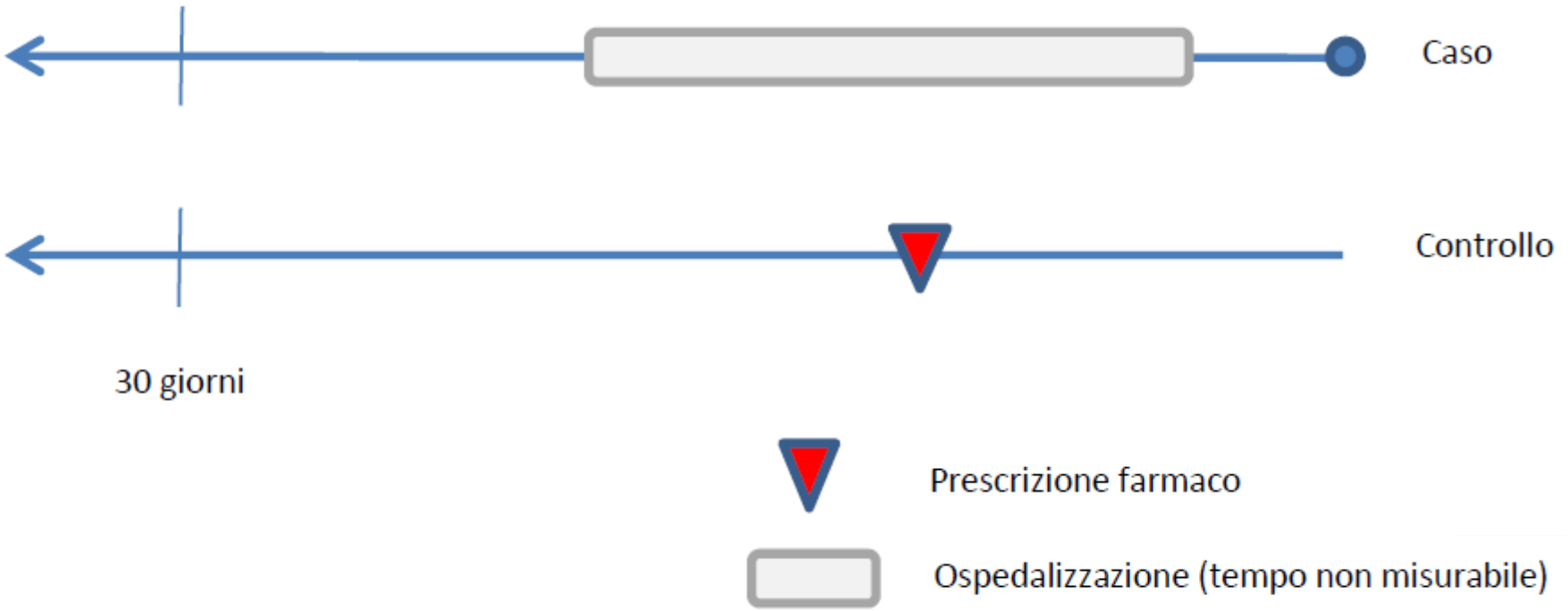
Immeasurable time-bias (2) – studio di coorte



modificato da Suissa et al.

Am J Epidemiol 2008;168:329–335

Immeasurable time-bias (3) – studio caso-controllo



modificato da Suissa et al.

Am J Epidemiol 2008;168:329–335

Immeasurable time-bias (4) - Esempio

Fluoroquinolones and the Risk of Serious Arrhythmia: A Population-Based Study

Francesco Lapi,[1,3,5] Machelle Wilchesky,[1,2] Abbas Kezouh,[1] Jacques I. Benisty,[1] Pierre Ernst,[1,4] and Samy Suissa[1,3]

[1]Centre for Clinical Epidemiology, Lady Davis Research Institute, Jewish General Hospital, [2]Donald Berman Maimonides Geriatric Centre, and Departments of [3]Epidemiology, Biostatistics and Occupational Health, and [4]Medicine, McGill University, Montreal, Quebec, Canada; and [5]Department of Preclinical and Clinical Pharmacology, University of Florence, Italy

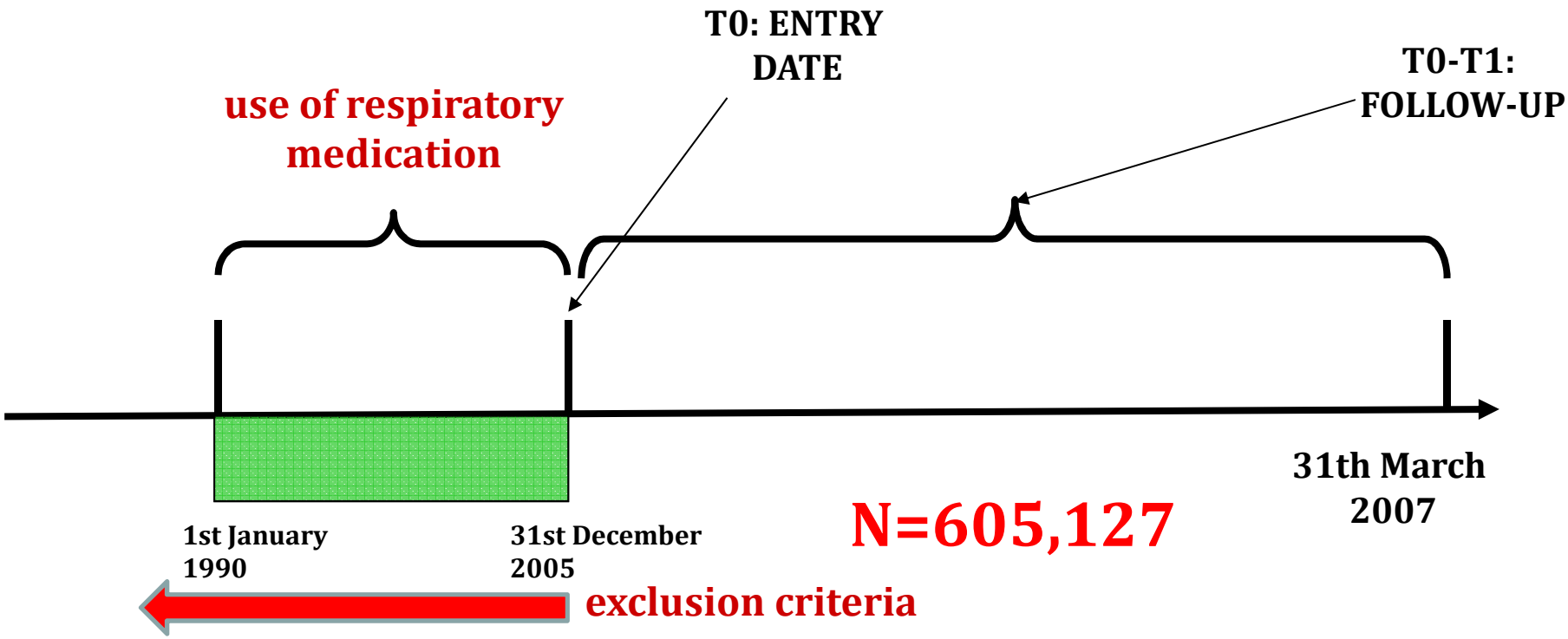
Clinical Infectious Diseases 2012;55(11):1457–65

Metodi (1) - Definizione della coorte

Exclusion criteria: ventricular or atrial arrhythmia at any diagnosis position (primary or otherwise) or medical services (ie, arrhythmia-related surgical/interventional procedures) or on recorded use of antiarrhythmic drugs

T0 (ENTRY DATE): prescription of respiratory drugs

T1 (EXIT DATE): ICD9/ICD10 (primary diagnosis) related to ventricular arrhythmia and sudden/unattended death (index date), death, data availability (31th Mar 2007)



Risultati (1)

Table 3. Crude and Adjusted Rate Ratios of Serious Arrhythmia for Current, Recent, and Past Use of Fluoroquinolones

	Cases (n = 1838)	Controls (n = 36 670)	Crude RR	Adjusted RR (95% CI)[a]
Recency of use, No. (%)[b]				
Current, new	20 (1.1)	215 (0.6)	2.04	1.62 (.97–2.71)
Current, not new	18 (1.0)	229 (0.6)	1.75	1.12 (.66–1.89)
All current	38 (2.1)	444 (1.2)	1.89	1.34 (.92–1.93)
Moxifloxacin	7 (0.4)	67 (0.2)	2.40	1.82 (.78–4.22)
Levofloxacin	5 (0.3)	69 (0.2)	1.66	0.78 (.29–2.13)
Ciprofloxacin	20 (1.1)	245 (0.7)	1.78	1.32 (.80–2.18)
Gatifloxacin	4 (0.22)	17 (0.05)	5.69	3.97 (1.15–13.62)
Others	2 (0.1)	46 (0.1)	0.93	0.83 (.19–3.60)
Recent	30 (1.6)	398 (1.1)	1.68	1.24 (.82–1.86)
Past	332 (18.1)	4778 (13.0)	1.53	1.14 (1.00–1.32)
Unexposed	1438 (78.2)	31 140 (84.7)	Reference	Reference

Abbreviations: CI, confidence interval; RR, rate ratio.

[a] Adjusted for all covariates reported in Table 1.

[b] Current: within 14 days before the index date; recent: 15–30 days before the index date; past: 31–365 days before the index date.

Clinical Infectious Diseases 2012;55(11):1457–65

Risultati (2)

Table 4. Crude and Adjusted Rate Ratios of Serious Arrhythmia for Current, Recent, and Past Use of Fluoroquinolones

	Cases (n = 1649)	Controls[a] (n = 36 051)	Crude RR	Adjusted RR (95% CI)[b]
Recency of use, No. (%)[c]				
Current, new	18 (1.1)	186 (0.5)	2.37	2.23 (1.31–3.80)
Current, not new	17 (1.0)	206 (0.6)	2.08	1.41 (.82–2.44)
All current	35 (2.1)	392 (1.1)	2.22	1.76 (1.19–2.59)
Moxifloxacin	7 (0.4)	56 (0.2)	3.30	3.30 (1.47–7.37)
Levofloxacin	3 (0.2)	61 (0.2)	1.30	1.29 (.40–4.17)
Ciprofloxacin	19 (1.2)	216 (0.6)	2.15	2.15 (1.34–3.46)
Gatifloxacin	4 (0.24)	15 (0.04)	7.40	7.38 (2.30–23.70)
Others	2 (0.1)	44 (0.1)	1.05	1.05 (.25–4.33)
Recent	26 (1.6)	372 (1.1)	1.70	1.26 (.80–1.93)
Past	295 (17.9)	4647 (12.9)	1.53	1.15 (1.00–1.34)
Unexposed	1293 (78.4)	30 640 (85.0)	Reference	Reference

Patients hospitalized during the current time window were excluded.

Abbreviations: CI, confidence interval; RR, rate ratio.

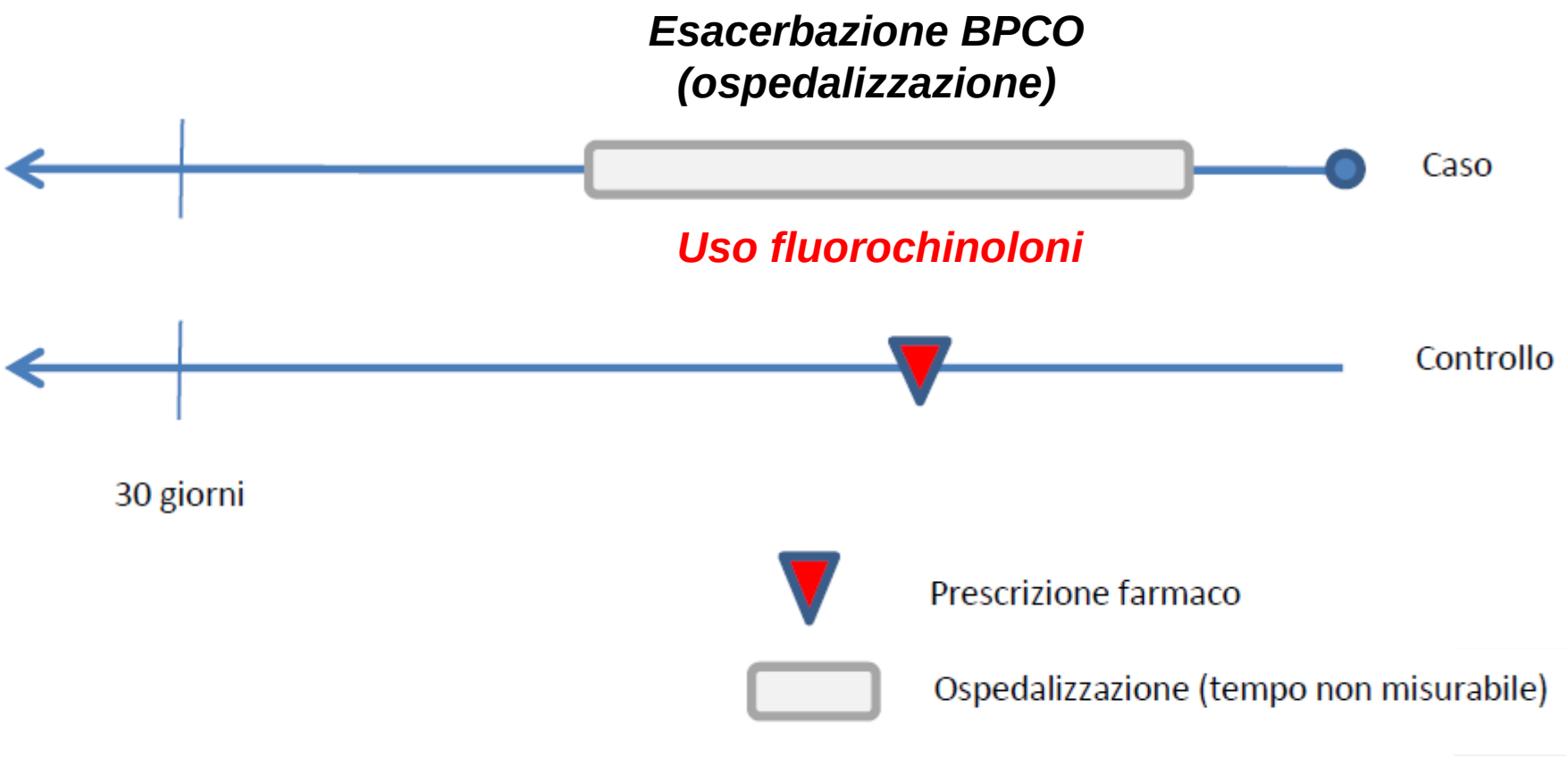
[a] Percentages are weighted for the number of controls being matched per case.

[b] Adjusted for all covariates reported in Table 1.

[c] Current: within 14 days before the index date; recent: 15–30 days before the index date; past: 31–365 days before the index date.

Clinical Infectious Diseases 2012;55(11):1457–65

Immeasurable time-bias - studio caso-controllo



modificato da Suissa et al.

Am J Epidemiol 2008;168:329–335

Immeasurable time-bias (5) - Esempio

TABLE 1. Characteristics of cases (deaths) and controls, according to inhaled corticosteroid prescription and hospitalization during the 30-day period prior to index date, selected from a cohort of 2,049 chronic obstructive pulmonary disease patients from Saskatchewan, Canada, 1990–1999

Inhaled corticosteroid prescription in the 30 days prior to the index date	Cases (deaths)		Controls	
	No.	Mean days hospitalized*	No.	Mean days hospitalized*
All subjects	1,313	11.0	1,313	2.3
Inhaled corticosteroid prescription	217	6.5	341	2.2
No inhaled corticosteroid prescription	1,096	11.9	972	2.3
Among subjects not hospitalized*				
Inhaled corticosteroid prescription	73	0	247	0
No inhaled corticosteroid prescription	290	0	719	0
Among subjects hospitalized*				
Inhaled corticosteroid prescription	144	9.9	94	8.1
No inhaled corticosteroid prescription	806	16.2	253	8.8

* Refers to hospitalizations spanning part or all of the 30-day period prior to the index date.

Am J Epidemiol 2008;168:329–335

Immeasurable time-bias (6) - Esempio

TABLE 2. Crude and adjusted rate ratios of death associated with current use of inhaled corticosteroids by different methods of data analysis with the cases (deaths) and controls selected from a cohort of 2,049 chronic obstructive pulmonary disease patients from Saskatchewan, Canada, 1990–1999

Inhaled corticosteroid use by method of data analysis	Cases	Controls	Crude rate ratio	Adjusted*	
				Rate ratio	95% confidence interval
No. of subjects	1,313	1,313			
Method 1—all subjects					
Use in the last 30 days	217	341	0.56	0.60	0.50, 0.73
No use in the last 30 days	1,096	972	1.00	1.00	Referent
Method 2—nonhospitalized subjects					
Use in the last 30 days	73	247	0.73	0.81	0.60, 1.10
No use in the last 30 days	290	719	1.00	1.00	Referent
Method 3—all subjects adjusted for hospitalization					
Use in the last 30 days	217	341	0.59	0.63	0.51, 0.79
No use in the last 30 days	1,096	972	1.00	1.00	Referent
Method 4—weighted by exposable time†					
Use in the last 30 days	169.6	315.5	0.73	0.79	0.64, 0.98
No use in the last 30 days	661.8	897.8	1.00	1.00	Referent
Method 5—weighted by exposable time in the unexposed†					
Use in the last 30 days	217	341	0.86	0.93	0.76, 1.14
No use in the last 30 days	661.9	897.9	1.00	1.00	Referent
Method 6—rate of exposure per 30 person-days	0.26	0.28	0.93	0.98	0.83, 1.17
Method 7—probability of exposure within 30 days obtained by the Kaplan-Meier product-limit estimator	0.36	0.32	1.21	1.35	1.14, 1.60

* Adjusted for age and sex.

† Frequencies weighted by exposable time correspond to the number of 30-day person-days.

Am J Epidemiol 2008;168:329–335

Conclusioni

Confondimento da indicazione

- non distorsione forte delle stime in studi di safety
- approcci analitici complessi (analisi di sensibilità)
- restrizione (approccio più semplice); limitazione: riduzione della potenza

Immeasurable time-bias

- semplice da identificare
- complesso da “risolvere”
- analisi di sensibilità per verificare la robustezza dei risultati