Disegno dello studio e tassonomia degli studi

Prof. Maria Grazia Valsecchi

Center of Biostatistics – University of Milano-Bicocca

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"

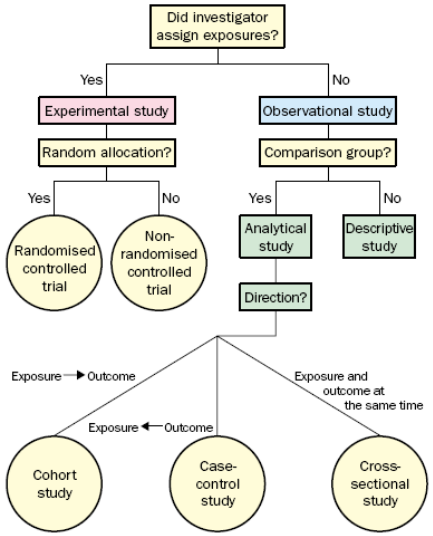
Una tassonomia degli studi nella ricerca clinica

- 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 sperimentali o osservazionali

L'esposizione è assegnata dal ricercatore?

Sì → **Studio Sperimentale**

Implica la manipolazione della esposizione (espressa da una o più variabili indipendenti) per studiare l'effetto sull' esito (espresso da una o più variabili dipendenti).
Il ricercatore "manipola" la esposizione

No → **Studio Osservazionale**

Si studia la relazione tra le differenze in una o più variabili in relazione a differenze in altre variabili senza che il ricercatore intervenga a modificare la esposizione.
Il ricercatore si limita ad osservare.

SE PARLIAMO più in generale di ESPOSIZIONE

Studi descrittivi

OSS

- Danno le informazioni iniziali in nuove aree:
  - frequenza di determinate caratteristiche/fattori;
  - Distribuzione geografica, temporale e demografica;
  - storia "naturale";
  - possibili determinanti di una condizione;
  - sorveglianza sanitaria
- I risultati:
  - Descrivono la distribuzione e le caratteristiche di una patologia e/o dei soggetti affetti;
  - Generano ipotesi di studio sull'eziologia (raramente sul trattamento)

Nella ricerca clinica spesso sono la descrizione di serie di casi

Examples of early leads from descriptive studies

Clinical observation	Underlying association
Hepatocellular adenoma in young women	Exposure to high-dose oral contraceptives
Blindness in newborn infants	High ambient oxygen concentrations in incubators
Kaposi's sarcoma in young men	Infection with HIV-1
Angiosarcoma of the liver in employees	Industrial exposure to vinyl chloride
Cataracts, heart defects, and deafness in newborns	Maternal infection with rubella during pregnancy

Un "Case report" che ha portato a scoprire una associazione:

A clinician reported benign hepatocellular adenomas, a rare tumour, in women who had taken oral contraceptives. *Schenken JR. Hepatocellular adenoma: relationship to oral contraceptives? JAMA 1976.*

A large case-control study pursued this lead and confirmed a strong association between long-term use of high-dose pills and this rare, but sometimes deadly, tumour. *Rooks JB, Ory HW, Ishak KG, et al. Epidemiology of hepatocellular adenoma: the role of oral contraceptive use. JAMA 1979*

Not all case reports deal with serious health threats; i.e. a temporal association is incorrectly inferred to be a causal one.

Case Series reports may suggest a false association:

Seven women in Pasadena (Ca) created controversy around the world in the late 1980s. The women had developed functional ovarian cysts while taking the new multiphasic oral contraceptive pills. *Am J Obstet Gynecol* 1987

Within 2 years, a publication showed no temporal association between the marketing of multiphasic pills and the number of women admitted to hospital for treatment of benign ovarian cysts (REAL WORLD STUDY). *Obstet Gynecol* 1989

5 years elapsed before cohort and case-control studies confirmed no association between multiphasic pills and ovarian cysts. *Am J Obstet Gynecol* 1992 and *Obstet Gynecol* 1992;

OSS

Studi analitici

Studiano la relazione tra esposizione ed esito

- Epidemiologia: relazione tra intensità di esposizione a fattori di rischio / protettivi e frequenza di malattia
- Epidemiologia clinica: impatto di un trattamento/procedura nella pratica clinica, fattori prognostici, effetti a lungo termine (farmacovigilanza)

Si differenziano per il legame dell'osservazione col tempo

oss

Studi analitici

Studio trasversale: guarda l'associazione di una esposizione con un esito misurati in contemporanea: spesso difficile interpretare causa-effetto

Studio caso-controllo: parte dall'esito e va retrospettivamente a misurare l' esposizione per vedere se vi è associazione

Studio di coorte: parte dalla misura dell'esposizione e valuta prospetticamente l'esito

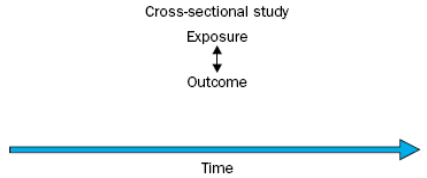
oss

Cross-sectional study

- Outcome (presence or absence of disease) and exposure are ascertained at the same time.
- Focus is on prevalence

Temporal (causal) relation might be unclear

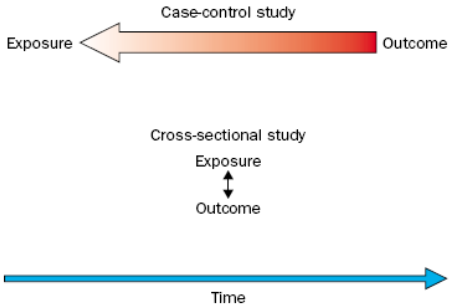
Ex.: a cross-sectional study finds obesity to be more common among women with than without arthritis. Did the extra weight load on joints lead to arthritis, or did women with arthritis become involuntarily inactive and then obese?



oss

Case-control study

- Starts with outcome and looks backward in time for exposure that might have caused the outcome
- Defines a group with an outcome (*cases*) and a group without (*controls*)
- Ascertains the prevalence of exposure to a risk factor in both groups
- If the prevalence of exposure is higher among cases, then the exposure is associated with an increased risk of the outcome



oss

Case-control study

Outbreaks of food-borne diseases on a cruise ship. Those with vomiting and diarrhoea are asked about food exposure, as are a sample of those not ill. If a higher proportion of those ill reports having eaten a food than those well, the food becomes suspect.

Case-control study

oss

Strenghts:

- useful for rare outcomes or that take a long time to develop
- requires less time, effort, and money than cohort study

Weaknesses:

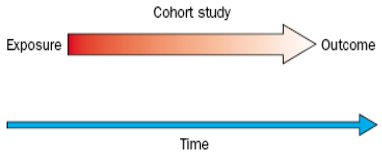
- choosing an appropriate control group
- recall bias (bias due to effect of memory)
- cannot calculate incidence rates, relative risk or attributable risk

Association is measured with ODDS RATIOS, good proxy for the true relative risk (especially if risk is relatively low)

Cohort study

oss

- **Proceeds from exposure to outcome**
- **Identifies a group with an exposure**
- **Follows the exposed and unexposed groups to determine outcomes**
- **If the exposed group develops a higher incidence than the unexposed, then exposure is associated with an increased risk of the outcome**



Cohort study

oss

Use of Proton Pump Inhibitors (PPI) is related to an increased risk of dementia in elderly?

A cohort of 73679 people aged ≥ 75 y and free of dementia at baseline was monitored for use of PPI and followed up. The 2950 patients receiving regular PPI medication had a significantly increased risk of incident dementia compared with those in the cohort not receiving PPI (70729 patients in the cohort).

Cohort study

Strenghts:

- Recall bias* is less of a concern
- Enables calculation of true incidence rates, relative risks and attributable risks
- Best for causal interpretation

Weaknesses:

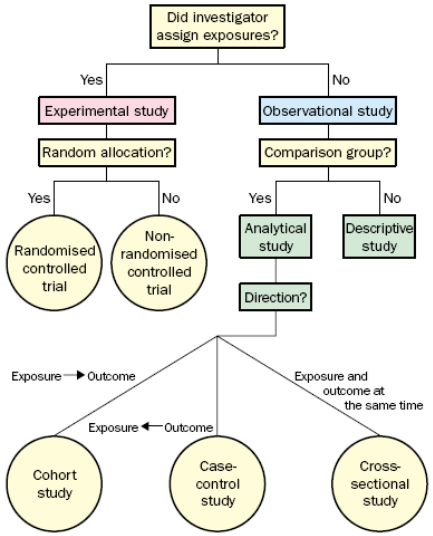
- Slow results with rare events or events that take years to develop
- Higher costs

Definitions

INCIDENT CASES: **new cases presenting the event of interest (diagnosis of dementia) in a given period of time**

PREVALENT CASES: **all cases who have a given characteristic (the event of interest, i.e. they have dementia) at the moment they are observed**

Clinical research has two large "kingdoms"



Studi sperimentali che riguardano il trattamento

SPER

In mancanza di un gruppo di controllo, non è possibile valutare se vi sia associazione trattamento-esito ovvero:

l'effetto di un trattamento (sperimentale)

è sempre quantificato relativamente ad un trattamento di controllo (standard o placebo)

NB: in generale, in uno studio osservazionale il confronto di outcome di trattamenti diversi non riflette solo l'effetto del trattamento stesso

Esposizione=trattamento

Studi sperimentali sul trattamento

SPER

Sono studi prospettici controllati in cui si definisce

gruppo di controllo

randomizzato

SI

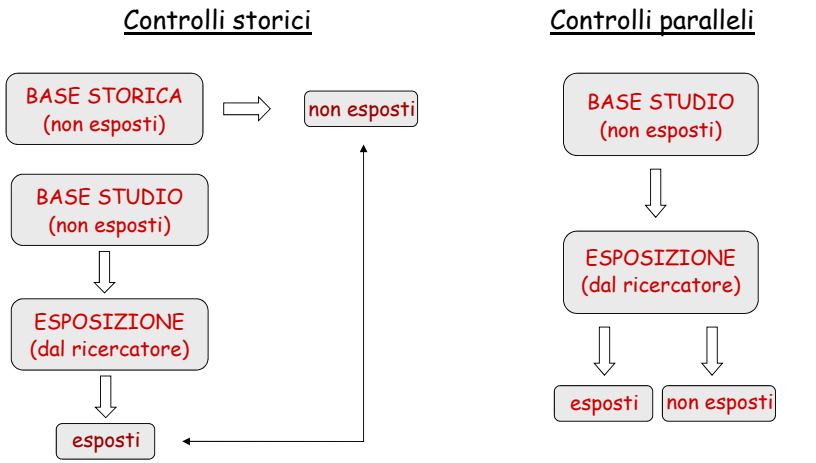
NO

Controlli concomitanti

Controlli storici

Studi sperimentali non randomizzati

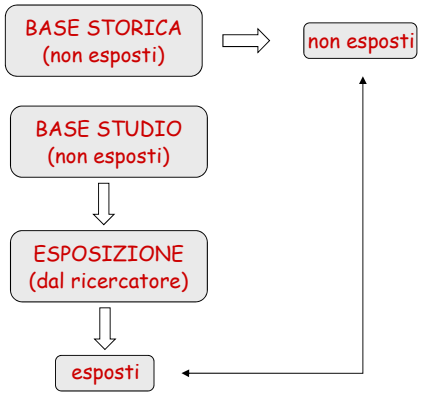
SPER



Il contrasto fra i gruppi confrontati stima l'effetto atteso del trattamento nei futuri malati

Studi con controlli storici

SPER



- I risultati vengono confrontati con pazienti simili osservati in precedenza nello stesso centro
- Rapido e poco costoso
- Altre fonti di dati storici:
  - Letteratura
  - Banche dati
- Si assume che i soggetti di controllo siano sovrapponibili ai soggetti esposti

E' veramente così?

Studi con controlli storici

SPER

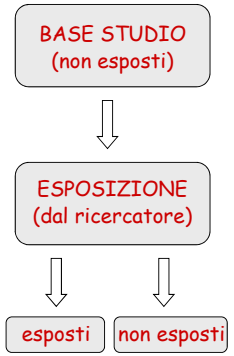
In realtà gli studi con controlli storici si prestano facilmente ad errori sistematici perché variazioni dell'esito nel tempo si possono avere per…

- variazioni nelle caratteristiche dei soggetti
- variazioni nei criteri di selezione dei soggetti
- variazioni nelle modalità di diagnosi e di assistenza dei pazienti
- variazioni nei criteri diagnostici
- variazioni nella qualità dei dati

Studi non randomizzati con controlli concomitanti

SPER

Controlli non randomizzati



- Bias di indicazione
- Preferenze del medico o del paziente
- Differenti modalità di assistenza

Il contrasto stima l'effetto atteso del trattamento nei futuri malati ?

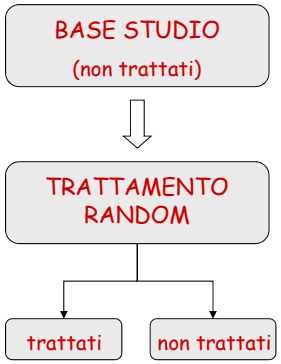
Studi randomizzati

SPER

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

I controlli sono per disegno concomitanti

Controlli randomizzati (RCT)



La randomizzazione

SPER

- 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

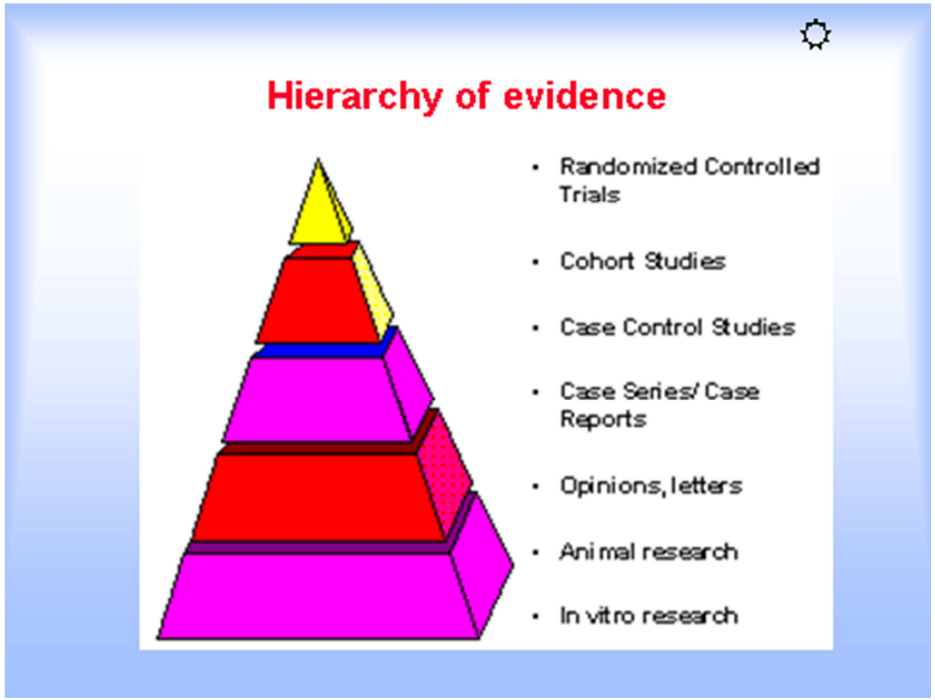
Avoids selection bias and confounding

Reduces information bias

Randomizzazione

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

Ci sono diverse tecniche per attuare la randomizzazione



In generale….

- Molte considerazioni metodologiche sono comuni agli studi sperimentali ed osservazionali….
- Entrambi i tipi di studio necessitano di un protocollo

CARATTERISTICHE DI UN BUON PIANO DI STUDIO

Un buon piano di studio, per portare a conclusioni **affidabili** e **riproducibili**, deve avere le seguenti caratteristiche:

- ✓ **Validità:**
  l'effetto osservato in corrispondenza di un trattamento (o esposizione) deve poter essere attribuito, senza ambiguità, al trattamento stesso
- ✓ **Precisione:**
  in uno studio valido, l'effetto osservato e quello vero differiscono a causa della variabilità casuale. Lo studio è tanto più preciso quanto più si riesce a limitare tale variabilità.
- ✓ **Applicabilità:**
  lo studio deve consentire di generalizzare le conclusioni.

CARATTERISTICHE DI UN BUON PIANO DI STUDIO

Validità: ⇒ **Randomizzazione**

Precisione: ⇒ **Dimensione campionaria**

Applicabilità ⇒ **Popolazione di riferimento? procedure? (criteri eleggibilità, modalità di applicazione del protocollo…)**

Precisione e potenza: disegno innovativo per un "large study"

Studio di "buona pratica clinica" mirato ad ottenere miglioramenti modesti, ma rilevanti per la pratica clinica.

Domanda: intensificazione della terapia di mantenimento con PULSES, già usati in passato, è utile nella moderna terapia della Leucemia Linfoblastica Acuta (LLA) in età pediatrica?

Studio Internazionale "PULSES" (1995-2000)
LLA a rischio intermedio (60% LLA pediatrica)

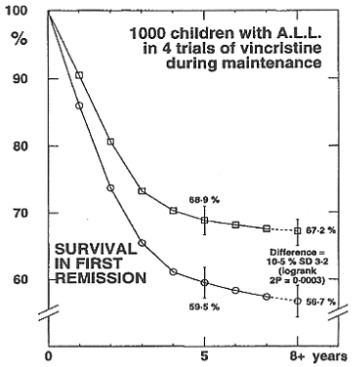
Childhood ALL Collaborative Group.Lancet 1996

Disegno della studio

PULSES: aggiunta di VCR+DXM

Intensificazione del mantenimento:

Meta-analysi di 5 studi randomizzati (1970-80)



Childhood ALL Collaborative Group. Lancet, 347: 1783-8, 1996

Disegno dello studio

Potenza

- **90% per mettere in evidenza una differenza δ=5%**
  rispetto al disease free survival del 79% a 4 anni del controllo
  2 interim, α=0.05, test a 2 code
- **target**: **2600 pazienti** randomizzati

Disegno innovativo

- **strategia PMA*: stessa domanda randomizzata in protocolli simili**
- controllo: **standard ottimale**
- 6 paesi Europei e 2 America Latina

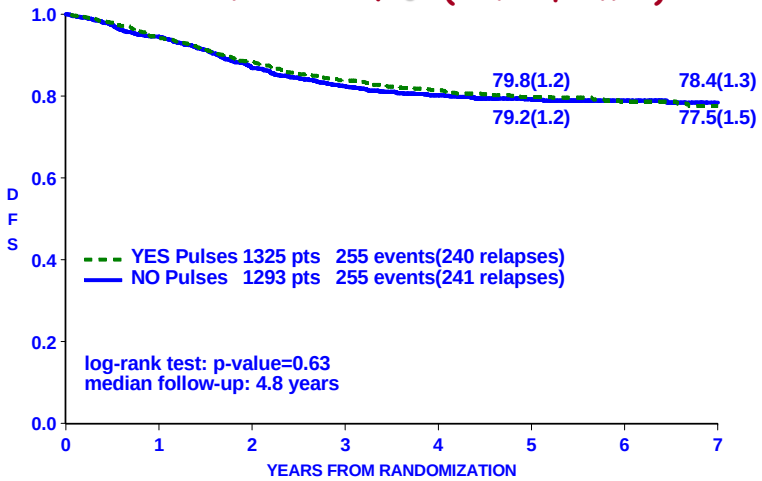
Analisi

- **modello stratificato a effetti fissi**

*Valsecchi-Masera, Ann. of Onc., 1996

Effetto dei PULSES

95% CI of δ: (-2.7%; 3.9%)



Conter, Valsecchi *et al.* Lancet 369:123-31, 2007

Strategia del disegno

	Esplicativo	*Pragmatico*
Primary objective	Increase knowledge	Give useful indications for clinical practice
Selection criteria	Very restrictive	Non restrictive
Generalizability of conclusions	Limited	Extended
Primary Endpoint	Clinical or surrogate	Clinical
Endpoint assessment	Intensively assessed	Asessed as by clinical practice
	Might work?	Does it work?

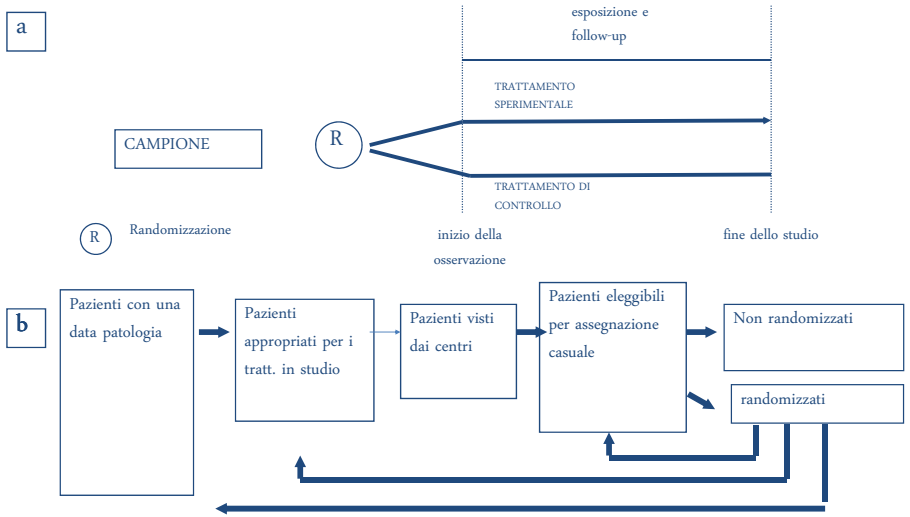
Criteri di inclusione

Poco selettivi	Molto selettivi
• Minore omogeneità dei malati	• Maggiore omogeneità dei malati
• Maggiore numerosità	• Minore numerosità
• Minore efficienza	• Maggiore efficienza
• Maggiore generalizzabilità	• Minore generalizzabilità

Criteri di esclusione

- rischio aggiuntivo non giustificato
- impraticabilità di almeno uno dei trattamenti
- difficoltà nei controlli del follow up
- scarsa disponibilità a collaborare
- (prevedibile ridotta aderenza al trattamento)
- (caratteristiche demografiche)

RAPPRESENTATIVITA'



Schema generale di uno studio clinico controllato (fig. a) e schema dell'ipotetico processo di selezione del campione randomizzato (frecce da sinistra a destra in fig. b) e di generalizzazione dei risultati (frecce da destra a sinistra, fig. b).

Processo ideale di un progetto clinico
(dopo esperimenti in vitro e animale)

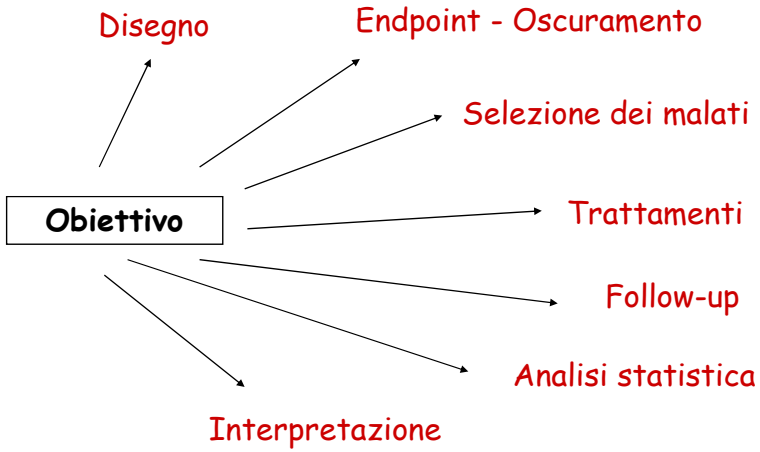
- **FARMACOCINETICA (dosi) e FARMACODINAMICA(meccanismo azione)**
- **STUDI DI FASE I**
- Profilo di safety del prodotto (generalmente ma non sempre) nel volontario sano.
- **STUDI DI FASE II**
- Profilo di safety nel prodotto nel paziente.
- Valutare l'attività del prodotto nelle condizioni cliniche ideali (ossia in condizioni sperimentali molto controllate).
- Definire gli "ingredienti" di base degli studi di fase III:
- - target population / dose/ dimensione campionaria
- **STUDI DI FASE III**
- Confermare l'efficacia del prodotto nelle condizioni cliniche reali.
- L'ipotesi da sottoporre a verifica è espressa in termini quantitativi.
- Le condizioni sperimentali adottate definiranno le condizioni in cui il prodotto è efficace e saranno riportate nel foglietto illustrativo se il prodotto sarà accettato.
- Gli studi di fase III dovranno essere almeno due, condotti indipendentemente, per dimostrare che i risultati sono riproducibili.

Un buon studio:

✓ **Pone una domanda importante e condivisa**

✓ **Vi risponde in modo affidabile**

L'aspetto più importante di uno studio e' il suo obiettivo primario



Guidelines for publication

Clinical trials - CONSORT

"The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials."

Lancet 2001 – BMJ 2004 – JAMA 2006 – Lancet 2008 – Ann Intern Med 2008

Observational studies - STROBE

"Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies."

BMJ 2007 – Lancet 2007 – Ann Intern Med 2007

Section/Topic	Item No	Checklist item
Title and abstract		
	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)

Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available

Esercitazione sui tipi di studio

Association of Proton Pump Inhibitors With Risk of Dementia
A Pharmacoepidemiological Claims Data Analysis

Willy Gomm, PhD; Klaus von Holt,MD, PhD; Friederike Thome, MSc; Karl Broich, MD;Wolfgang Maier, MD; Anne Fink, MSc; Gabriele Doblhammer, PhD; Britta Haenisch, PhD

IMPORTANCE Medications that influence the risk of dementia in the elderly can be relevant for dementia prevention. Proton pump inhibitors (PPIs) are widely used for the treatment of gastrointestinal diseases but have also been shown to be potentially involved in cognitive decline.
OBJECTIVE To examine the association between the use of PPIs and the risk of incidentdementia in the elderly.

DESIGN, SETTING, AND PARTICIPANTS We conducted a prospective cohort study using observational data from 2004 to 2011, derived from the largest German statutory health insurer, Allgemeine Ortskrankenkassen (AOK). Data on inpatient and outpatient diagnoses (coded by the German modification of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*) and drug prescriptions (categorized according to the Anatomical Therapeutic Chemical Classification System) were available on a quarterly basis. Data analysis was performed from August to November 2015.

EXPOSURES Prescription of omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole.
MAIN OUTCOMES AND MEASURES The main outcomewas a diagnosis of incident dementia coded by the German modification of the *International Statistical Classification of Diseasesand Related Health Problems, Tenth Revision*. The association between PPI use and dementia was analyzed using time-dependent Cox regression. The model was adjusted for potential confounding factors, including age, sex, comorbidities, and polypharmacy.
RESULTS A total of 73 679 participants 75 years of age or older and free of dementia at baseline were analyzed. The patients receiving regular PPI medication (n = 2950; mean [SD] age, 83.8 [5.4] years; 77.9%female) had a significantly increased risk of incident dementia compared with the patients not receiving PPI medication (n = 70 729; mean [SD] age, 83.0 [5.6] years; 73.6%female) (hazard ratio, 1.44 [95%CI, 1.36-1.52]; *P* < .001).
CONCLUSIONS AND RELEVANCE The avoidance of PPI medication may prevent the development of dementia. This finding is supported by recent pharmacoepidemiological analyses on primary data and is in line with mouse models in which the use of PPIs increased the levels of β-amyloid in the brains of mice. Randomized, prospective clinical trials are needed to examine this connection in more detail.

JAMA Neurol. 2016;73(4):410-416. doi:10.1001/jamaneurol.2015.4791

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

Stephen Hulley, MD; et al.for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group

Context.—Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials.

Objective.—To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease.

Design.—Randomized, blinded, placebo-controlled secondary prevention trial.

Setting.—Outpatient and community settings at 20 US clinical centers.

Participants.—A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years.

Intervention.—Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and75%at the end of 3 years.

Main Outcome Measures.—The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated
cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered.

Results.—Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and10%higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (eachP,.001). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, 2.89; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08; 95% CI, 0.84-1.38). **Conclusions.—**During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue.

JAMA. 1998;280:605-613

Food Groups and Alcoholic Beverages and the Risk of Stomach Cancer: A Case-Control Study in Italy

E. Lucenteforte, et al.

To investigate the role of a wide range of foods and beverages on the risk of stomach cancer, we analyzed data from a case-control study carried out in Italy between 1997 and 2007 on 230 subjects with incident histologically confirmed stomach cancer (143 men and 87 women, age range 22–80 yr) and 547 controls (286 men and 261women, age range 22–80 yr) admitted to hospital for acute, nonneoplastic diseases. Odds ratios (OR) of stomach cancer and their corresponding 95% confidence intervals (CI) were estimated using unconditional multiple logistic regression models, adjusted for age,sex, energy intake, and other selected variables. A direct association with stomach cancer riskwas observed for cereals (OR=2.07, 95% CI = 1.01–4.24, for the highest compared to the lowest quintile of intake, *P* for trend = 0.03), soups (OR = 1.94, 95% CI = 1.10–3.42, *P* for trend = 0.05), and potatoes (OR = 2.04, 95% CI = 1.05–3.98, *P* for trend = 0.04). Conversely, inverse trends in risk were observed with vegetables (OR = 0.47, 95% CI = 0.27–0.81, *P* for trend = 0.01) and fruit intake (OR = 0.53, 95% CI = 0.30–0.93, *P* for trend = 0.08). The results of this study confirm a protective role of vegetables and fruit against stomach cancer and suggest a detrimental effect of (refined) cereals on this neoplasm.

Nutrition and Cancer, 60(5), 577–584, 2008

Real world study comparing commonly prescribed COPD medicines shows choice of treatment has impact on patient outcomes

Tuesday, 19 March 2013

AstraZeneca today announced that an analysis of data from real world study PATHOS, published in the Journal of Internal Medicine, show that chronic obstructive pulmonary disease (COPD) patients treated with SYMBICORT® Turbuhaler® (budesonide/formoterol) are significantly less likely to suffer from COPD-related exacerbations – or ‘flare ups’ – and are significantly less likely to be hospitalised for COPD than those treated with SERETIDE™ (fluticasone/salmeterol).1 PATHOS is the largest real world study to compare the effectiveness of two commonly prescribed inhaled corticosteroid and long-acting beta agonist (ICS/LABA) combination treatments for COPD with more than one year of patient follow up.

Combination of budesonide/formoterol more effective than fluticasone/salmeterol in preventing exacerbations in chronic obstructive pulmonary disease: the PATHOS study.

Larsson K, Janson C, Lisspers K, Jørgensen L, Stratelis G, Telg G, Ställberg B, Johansson - Karolinska Institutet, Stockholm, Sweden. kjell.larsson@ki.se

Abstract

OBJECTIVES: Combinations of inhaled corticosteroids (ICSs) and long-acting β2 -agonists (LABAs) are recommended for patients with moderate and severe chronic obstructive pulmonary disease (COPD). However, it is not known whether different fixed combinations are equally effective. The aim of this study was to investigate exacerbation rates in primary care patients with COPD treated with budesonide/formoterol compared with fluticasone/salmeterol.

METHODS: Patients with physician-diagnosed COPD and a record of postdiagnosis treatment with a fixed combination of budesonide/formoterol or fluticasone/salmeterol were included. Data from primary care medical records were linked to those from Swedish national hospital, drug and cause of death registers. Pairwise (1 : 1) propensity score matching was carried out at the index date (first prescription) by prescribed fixed ICS/LABA combination. Exacerbations were defined as hospitalizations, emergency visits and collection of oral steroids or antibiotics for COPD. Yearly event rates were compared using Poisson regression.

RESULTS: Matching of 9893 patients (7155 budesonide/formoterol and 2738 fluticasone/salmeterol) yielded two cohorts of 2734 patients, comprising 19 170 patient-years. The exacerbation rates were 0.80 and 1.09 per patient-year in the budesonide/formoterol and fluticasone/salmeterol groups, respectively (difference of 26.6%; $P < 0.0001$); yearly rates for COPD-related hospitalizations were 0.15 and 0.21, respectively (difference of 29.1%; $P < 0.0001$). All other healthcare outcomes were also significantly reduced with budesonide/formoterol versus fluticasone/salmeterol.

CONCLUSIONS: Long-term treatment with fixed combination budesonide/formoterol was associated with fewer healthcare utilization-defined exacerbations than fluticasone/salmeterol in patients with moderate and severe COPD.