GIMBE®

Gruppo Italiano per la Medicina Basata sulle Evidenze

Evidence-Based Medicine Italian Group

Workshop

Evidence-based Medicine

Le opportunità di un linguaggio comune 3ª ed.

Como, 1-2 aprile 2006

Sezione di Como

Workshop metodologico

L'effetto classe: quando due farmaci sono realmente simili?

Nino Cartabellotta

1. Cosa definisce l'effetto classe dei farmaci?

1. Analoga struttura chimica
2. Analogo meccanismo d'azione
3. Analoghi effetti farmacologici
4. Analoghi risultati (efficacia-effetti collaterali)

Evidence-Based Medicine Working Group

Users' Guides To Biomedical Literature

Applying clinical trial results. B. Guidelines for determining whether a drug is exerting (more than) a class effect

JAMA 1999;282:771-8

L'applicazione dei risultati dei trial clinici

B. Linee guida per decidere se l'effetto di un farmaco è simile (o superiore) a quello dei farmaci della stessa classe farmacologica

Users' Guides to the Medical Literature

• Nonostante non ci sia una definizione uniformemente accettata di classe “farmacologica” è accettato che i farmaci appartengono alla stessa classe per uno dei tre motivi elencati nella tabella 1.

Tabella 1 - Definizioni di classi farmacologiche

Definizione	Esempio
Farmaci con analoga struttura chimica	diidropiridina - i calcioantagonisti hanno anelli diidropiridinici
Farmaci con analogo meccanismo d’azione	i calcioantagonisti bloccano i canali del calcio voltaggio-dipendenti sulle superfici delle membrane cellulari
Farmaci con analoghi effetti farmacologici	gli antipertensivi (calcioantagonisti, ACE-inibitori, beta-bloccanti, tiazidici, afla-bloccanti) abbassano la pressione arteriosa

JAMA, 1999

E i risultati ?

Furberg CD

Class Effects and Evidence-Based Medicine

Clin Cardiol 2003;23(Suppl. IV):15-19

• Drugs grouped into a therapeutic class on the basis of a common mechanism of action often have considerably different pharmacodynamic and pharmacokinetic properties.

• Among ACE inhibitors, differences with potential clinical relevance include:

- potency
- whether the drug is an active compound or requires metabolic activation
- lipophilicity
- route(s) of elimination
- half-life.

Furberg CD. Clin Cardiol 2000

Table I Selected pharmacokinetic parameters of angiotensin-converting enzyme (ACE) inhibitors

ACE inhibitor	Lipophilicity	t_{max} (h)	Half-life (h)	Elimination route
Benazepril	+	1.5	21.0	Renal + hepatic
Captopril	+	1.0	2.0	Renal
Enalapril	++	4.0	11.0	Renal
Fosinopril	+++	3.0	12.0	Renal + hepatic (50/50)
Lisinopril	0	7.0	13.0	Renal
Perindopril	+	4.0	9.0	Renal
Quinapril	++	2.0	3.0	Renal
Ramipril	+	3.0	12.0	Renal + hepatic (70/30)
Spirapril	+	2.5	30.0	Renal + hepatic (50/50)
Trandolapril	++	4.0	16–24	Renal + hepatic (30/70)

Abbreviations: ACE = angiotensin-converting enzyme, t_{max} = time to reach maximum plasma concentration, + = slight, ++ = moderate, +++ = high.
Adapted from Ref. No. 4 with permission.

Furberg CD. Clin Cardiol 2000

• Large clinical trials have documented the clinical benefits of several ACE inhibitors in various patient populations, and many clinical effects are likely to be the same.

• However, there are possible quantitative differences among ACE inhibitors that may alter the overall therapeutic benefits for specific patient populations and indications, and “equipotency” in terms of clinical efficacy is difficult to determine.

Furberg CD. Clin Cardiol 2000

- Since the concept of "class effect" is a term of convenience that has no universally accepted definition and subsequently should not form the basis for the practice of EBM, untested drugs of a "class" should be considered to be unproven drugs.

Furberg CD. Clin Cardiol 2000

2. Ritieni che tutti i farmaci di una stessa “classe” siano supportati da analoghe prove di efficacia?

1. No
2. Sì

- Several ACE inhibitors have been shown to reduce the risk of cardiovascular morbidity and mortality in patients with cardiovascular disease.

- They are currently indicated for the treatment of patients with hypertension,particularly those with diabetes, and postinfarction patients with left ventricular dysfunction or congestive heart failure.

- However, none of the commercially available ACE inhibitors have been studied in all of these patient populations in large clinical trials and the magnitude of the benefit demonstrated with each ACE inhibitor varies among trials.

Furberg CD. Clin Cardiol 2000

Table II Large clinical trials documenting effects of angiotensin-converting enzyme (ACE) inhibitors.[1, 6-21]				
	Clinical trial			
ACE inhibitor	**CHF/LVD**	**MI/CHD**	**HPT**	**Type 2 Diabetes**
Benazepril	0	0	0	0
Captopril	SAVE	SAVE/ISIS-4	CAPPP	0
Enalapril	SOLVD	SOLVD	0	ABCD
	CONSENSUS			
Fosinopril	0	0	0	FACET
Lisinopril	ATLAS	GISSI-3	0	0
Perindopril	0	0	0	0
Quinapril	0	0	0	0
Ramipril	AIRE	AIRE/HOPE	HOPE	HOPE
Spirapril	0	0	0	0
Trandolapril	TRACE	TRACE	0	0

Furberg CD. Clin Cardiol 2000

3. Ritieni che tutti farmaci di una stessa “classe” abbiano lo stesso profilo di sicurezza?

1. No
2. Sì

Pedersen T, Gaw A

Statins: similarities and differences

Am J Manag Care 2001;7(5 Suppl):S132-7

- The number of statins available to physicians continues to grow, leading to the question: Are all statins alike?

- Comparisons of side effects and safety profiles and the dose-response relationship among the different drugs show similar results.

- On the other hand, the molecular structures of the newer statins are not similar and could have an effect on the mechanism of action of the compounds.

- Differences in metabolism also suggest the possibility of serious drug-drug interactions

Pedersen T, et al. Am J Manag Care 2001

Agosto 2001
RCTs sulle statine con end-point rilevanti

	Prevenzione primaria	Prevenzione secondaria
Simvastatina	-	4S
Pravastatina	WOSCOPS	CARE, LIPID
Lovastatina	AFCAPS/TexCAPS	-
Cerivastatina	-	-
Fluvastatina	-	-
Atorvastatina	-	-

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B. Linee guida per decidere se l'effetto di un farmaco è simile (o superiore) a quello dei farmaci della stessa classe farmacologica

Users' Guides to the Medical Literature

Tabella 2 - Livelli di evidenza per confronti di efficacia dei farmaci all'interno della stessa classe

Livello	Confonto	Pz.allo studio	Esiti
1	Diretto tra farmaci (all'interno di un RCT *head to head*)	Identici (per definizione)	Clinicamente importanti

ESEMPIO

- RCT di confronto ninostatina vs giannistatina
- End-point. Mortalità coronarica, eventi coronarici non fatali

JAMA, 1999

Tabella 2 - Livelli di evidenza per confronti di efficacia dei farmaci all'interno della stessa classe

Livello	Confonto	Pz.allo studio	Esiti
2a	Diretto tra farmaci (all'interno di un RCT *head to head*)	Identici (per definizione)	Surrogati, di riconosciuta validità

ESEMPIO

- RCT di confronto ninostatina vs giannistatina
- End-point. Riduzione placche aterosclerotiche, LDL-C (?)

JAMA, 1999

Tabella 2 - Livelli di evidenza per confronti di efficacia dei farmaci all'interno della stessa classe

Livello	Confonto	Pz.allo studio	Esiti
2 b	Tra RCT di farmaci diversi vs placebo	Simili, o differenti (nello stato di malattia e nei fattori di rischio)	Clinicamente importanti, oppure surrogati, di riconosciuta validità

ESEMPIO

- RCT di confronto ninostatina vs placebo
- RCT di contronto giannistatina vs placebo
- End-point
  - Mortalità coronarica, eventi coronarici non fatali
  - Riduzione placche aterosclerotiche, LDL-C (?)

JAMA, 1999

Tabella 2 - Livelli di evidenza per confronti di efficacia dei farmaci all'interno della stessa classe

Livello	Confonto	Pz.allo studio	Esiti
3	Tra RCT di farmaci diversi vs placebo	Simili o differenti	Surrogati di non riconosciuta validità

ESEMPIO

- RCT di confronto ninostatina vs placebo
- RCT di contronto giannistatina vs placebo
- End-point. Valori di LDL colesterolo

JAMA, 1999

Tabella 2 - Livelli di evidenza per confronti di efficacia dei farmaci all'interno della stessa classe

Livello	Confonto	Pz.allo studio	Esiti
4	Tra studi non randomizzati (osservazionali, ricerche su database amministrativi)	Simili o differenti	Clinicamente importanti

ESEMPIO

- Confronto tassi "aggiustati" di mortalità coronarica e/o di eventi coronarici non fatali tra:
  - pazienti trattati con ninostatina
  - pazienti trattati con giannistatina

JAMA, 1999

Tabella 2 - Livelli di evidenza per confronti di efficacia dei farmaci all'interno della stessa classe

Livello	Confonto	Pz.allo studio	Esiti
4	Tra studi non randomizzati (osservazionali, ricerche su database amministrativi)	Simili o differenti	Clinicamente importanti

PROBLEMI

- Confondimento dovuto alle indicazioni, alla compliance
- Presenza di confondenti non noti o non misurati
- Errori di misura
- Database limitati, sistemi di codifica non utilizzabili per la ricerca

JAMA, 1999

Mortality Rates in Elderly Patients Who Take Different Angiotensin-Converting Enzyme Inhibitors after Acute Myocardial Infarction: A Class Effect?

Louise Pilote, MD, MPH, PhD; Michal Abrahamowicz, PhD; Eric Rodrigues, MSc; Mark J. Eisenberg, MD, MPH; and Elham Rahme, PhD

Background: Several randomized, controlled trials show that angiotensin-converting enzyme (ACE) inhibitors improve survival in patients who have had an acute myocardial infarction. However, existing data from trials do not address whether all ACE inhibitors benefit patients similarly.

Objective: To evaluate whether all ACE inhibitors are associated with similar mortality in patients 65 years of age or older who have had an acute myocardial infarction.

Design: Retrospective cohort study that used linked hospital discharge and prescription databases containing information on 18 453 patients 65 years of age or older who were admitted for an acute myocardial infarction between 1 April 1996 and 31 March 2000.

Setting: 109 hospitals in Quebec, Canada.

Patients: 7512 patients who filled a prescription for an ACE inhibitor within 30 days of discharge and who continued to receive the same drug for at least 1 year.

Measurements: The association between the specific drugs and clinical outcomes was measured by using Cox proportional hazards models, with adjustment for demographic, clinical, physician, and hospital variables and dosage categories, represented by time-dependent variables.

Results: Enalapril, fosinopril, captopril, quinapril, and lisinopril were associated with higher mortality than was ramipril; the adjusted hazard ratios and 95% CIs were 1.47 (95% CI, 1.14 to 1.89), 1.71 (CI, 1.29 to 2.25), 1.56 (CI, 1.13 to 2.15), 1.58 (CI, 1.10 to 2.82), and 1.28 (CI, 0.98 to 1.67), respectively. The adjusted hazard ratio associated with perindopril was 0.98 (CI, 0.60 to 1.60).

Limitations: The administrative databases did not contain detailed clinical information, and unmeasured factors associated with a patient's risk for death may have influenced physicians' prescription choices.

Conclusion: Survival benefits in the first year after acute myocardial infarction in patients 65 years of age or older seem to differ according to the specific ACE inhibitor prescribed. Ramipril was associated with lower mortality than most other ACE inhibitors.

Ann Intern Med. 2004;141:102-112. www.annals.org

For author affiliations, see end of text.

See editorial comment on pp 157-158.

Effectiveness of statins for secondary prevention in elderly patients after acute myocardial infarction: an evaluation of class effect

Zheng Zhou, Elham Rahme, Michal Abrahamowicz, Jack V. Tu, Mark J. Eisenberg, Karin Humphries, Peter C. Austin, Louise Pilote

CMAJ 2005;172(9):1187-94

Background: Clinical trials have shown the benefits of statins after acute myocardial infarction (AMI). However, it is unclear whether different statins exert a similar effect in reducing the incidence of recurrent AMI and death when used in clinical practice.

Methods: We conducted a retrospective cohort study (1997–2002) to compare 5 statins using data from medical administrative databases in 3 provinces (Quebec, Ontario and British Columbia). We included patients aged 65 years and over who were discharged alive after their first AMI-related hospital stay and who began statin treatment within 90 days after discharge. The primary end point was the combined outcome of recurrent AMI or death from any cause. The secondary end point was death from any cause. Adjusted hazard ratios (HRs) for each statin compared with atorvastatin as the reference drug were estimated using Cox proportional hazards regression analysis.

Results: A total of 18 637 patients were prescribed atorvastatin (n = 6420), pravastatin (n = 4480), simvastatin (n = 5518), lovastatin (n = 1736) or fluvastatin (n = 483). Users of different statins showed similar baseline characteristics and patterns of statin use. The adjusted HRs (and 95% confidence intervals) for the combined outcome of AMI or death showed that each statin had similar effects when compared with atorvastatin: pravastatin 1.00 (0.90–1.11), simvastatin 1.01 (0.91–1.12), lovastatin 1.09 (0.95–1.24) and fluvastatin 1.01 (0.80–1.27). The results did not change when death alone was the end point, nor did they change after adjustment for initial daily dose or after censoring of patients who switched or stopped the initial statin treatment.

Interpretation: Our results suggest that, under current usage, statins are equally effective for secocondary prevention in elderly patients after AMI.

Zhou Z, et al. CMAJ, 2005

Table 1. Levels of Evidence for Comparing the Efficacy of Drugs within the Same Class*

Level	Comparison	Study Patients	Outcomes
1	Within a "head-to-head" randomized trial	Identical (by definition)	Clinically important outcomes
2A	Within a "head-to-head" randomized trial	Identical (by definition)	Validated surrogate outcomes
2B	Across randomized trials of different drugs versus placebo	Similar or different (in disease and risk factor status)	Clinically important outcomes or validated surrogate outcomes
3A	Across subgroup analyses from randomized trials of different drugs versus placebo	Similar or different	Clinically important outcomes or surrogate outcomes
3B	Across randomized trials of different drugs versus placebo	Similar or different	Unvalidated surrogate outcomes
3C	Between nonrandomized studies (observational studies and administrative database research)	Similar or different	Clinically important outcomes

Active-Control Equivalence Trials and Antihypertensive Agents

Finlay A. McAlister, MD, MSc, David L. Sackett, MD, MSc

PURPOSE: To identify methodological features that affect the validity of conclusions drawn from active-control equivalence trials and to apply these criteria to recently published trials comparing antihypertensive agents from different classes.

METHODS: Standard methodological criteria for randomized clinical trials and six additional methodological features that affect the validity of active-control equivalence trials were applied to four recently published large trials that compared different antihypertensive classes and that concluded that their results showed equivalence.

RESULTS: All four of these trials fulfilled standard criteria for randomized trials. However, none fulfilled all of the six additional methodological criteria that affect the validity of active-control equivalence trials, one fulfilled five criteria, two fulfilled two criteria, and one failed to fulfill any of the criteria.

CONCLUSION: Standard methodological criteria for evaluating superiority trials are inadequate for the interpretation of active-control equivalence trials. The methodological criteria outlined in this article for judging the validity of active-control equivalence trials are not specific to antihypertensive trials and may be applied to trials that test a wide variety of interventions.

Am J Med. 2001;111:553–558.

Tabella 4 - Livelli di evidenza nell'analisi comparativa sulla sicurezza dei farmaci all'interno della stessa classe

Livello	Tipo di studio	Vantaggi	Fattori in grado di minare la validità dello studio
1	RCT	L'unico tipo di disegno che consenta di scoprire effetti avversi quando essi siano simili all'evento che il trattamento sta cercando di prevenire	Può non avere potenza sufficiente per evidenziare gli effetti avversi
2	Coorte	Raccolta prospettica dei dati, coorte definita	È criticamente dipendente dall'accuratezza di follow-up, classificazione e misurazione
3	Caso-controllo	Poco costoso e rapido da eseguire	Possibili bias di selezione e di ricordo; le relazioni temporali possono non essere chiare
4	Fase 4	Se di dimensione sufficientemente ampia, può evidenziare effetti avversi rari, ma importanti	Assenza di gruppo di controllo, o di appaiamento (*matching*); è criticamente dipendente dall'accuratezza di follow-up, classificazione e misurazione
5	Serie di casi	Poco costoso e rapido da eseguire	Piccola dimensione campionaria, bias di selezione, assenza di gruppo di controllo
6	Report di casi	Poco costoso e rapido da eseguire	Piccola dimensione campionaria, bias di selezione, assenza di gruppo di controllo

JAMA, 1999

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• Tolman KG. Thiazolidinedione hepatotoxicity: a class effect? Int J Clin Pract Suppl. 2000 Oct;(113):29-34.