# ¿Necesitamos para algo los antinflamatorios selectivos COX-2 (celecoxib, etoricoxib)?

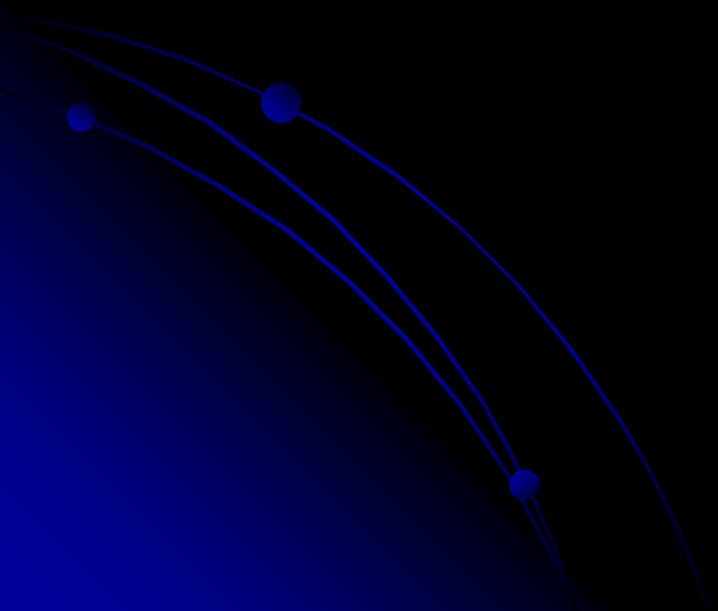
Mayo 2009

Javier Garjón Parra

Sº Prestaciones Farmacéuticas

Servicio Navarro de Salud
Osasunbidea

# Una historia convulsa



# ROFECOXIB

2000

Se publica el ensayo VIGOR en pacientes con artritis reumatoide que muestra más riesgo de infarto con rofecoxib que con naproxeno. Los autores sugieren que el naproxeno puede tener efecto protector.

(Bombardier et al. New Engl J Med. 343: 1520-8)

The New England Journal of Medicine

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H., RUBEN BURGOS-VARGAS, M.D., BARRY DAVIS, M.D., PH.D., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D., CHRISTOPHER J. HAWKEY, M.D., MARC C. HOCHBERG, M.D., TORE K. KVIEN, M.D., AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

ABSTRACT

*Background* Each year, clinical upper gastrointestinal events occur in 2 to 4 percent of patients who are taking nonselective nonsteroidal antiinflammatory drugs (NSAIDs). We assessed whether rofecoxib, a selective inhibitor of cyclooxygenase-2, would be associated with a lower incidence of clinically important upper gastrointestinal events than is the nonselective NSAID naproxen among patients with rheumatoid

NONSTEROIDAL antiinflammatory drugs (NSAIDs) are among the most commonly used medications in the world.[1] A major factor limiting their use is gastrointestinal toxicity. Although endoscopic studies reveal that gastric or duodenal ulcers develop in 15 to 30 percent of patients who regularly take NSAIDs,[2] the chief concern is clinically important gastrointestinal problems, such as bleeding. It has been estimated that more than

# ROFECOXIB

2004

El estudio APPROVE se interrumpe debido a un exceso de un evento trombótico por cada 139 pacientes-año tratados con rofecoxib. (*Mamdani et al. Arch Intern Med. 163: 481-6*)

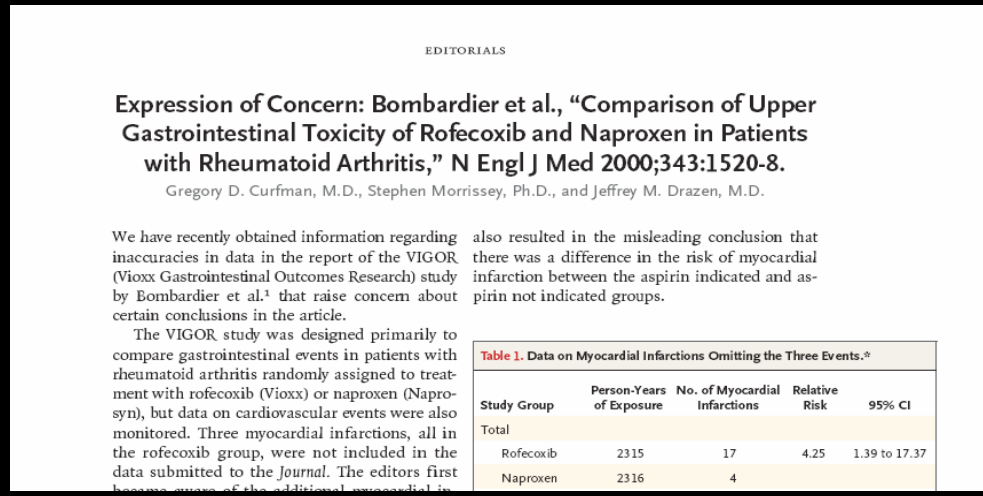
Retirada del rofecoxib en todo el mundo.

# ROFECOXIB

2005

La revista **N Engl J Med** publica un editorial de expresión de inquietud (*Expression of Concern* **)** debido a que en los datos de la publicación original del estudio VIGOR se dejaron de comunicar tres infartos de miocardio, llevando a conclusiones incorrectas.

(Curfman et al. N Engl J Med ;353: 2813-4)



EDITORIALS

**Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," N Engl J Med 2000;343:1520-8.**

Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., and Jeffrey M. Drazen, M.D.

We have recently obtained information regarding inaccuracies in data in the report of the VIGOR (Vioxx Gastrointestinal Outcomes Research) study by Bombardier et al.[1] that raise concern about certain conclusions in the article.

The VIGOR study was designed primarily to compare gastrointestinal events in patients with rheumatoid arthritis randomly assigned to treatment with rofecoxib (Vioxx) or naproxen (Naprosyn), but data on cardiovascular events were also monitored. Three myocardial infarctions, all in the rofecoxib group, were not included in the data submitted to the *Journal*. The editors first

also resulted in the misleading conclusion that there was a difference in the risk of myocardial infarction between the aspirin indicated and aspirin not indicated groups.

Table 1. Data on Myocardial Infarctions Omitting the Three Events.*

| Study Group | Person-Years of Exposure | No. of Myocardial Infarctions | Relative Risk | 95% CI |
|---|---|---|---|---|
| Total | | | | |
| Rofecoxib | 2315 | 17 | 4.25 | 1.39 to 17.37 |
| Naproxen | 2316 | 4 | | |

- El VALDECOXIB se retira del mercado en 2005 (no se llega a comercializar en España) por riesgo cardiovascular y reacciones dermatológicas algunas de ellas mortales, (eritema multiforme, dermatitis exfoliativa, síndrome de Stevens-Johnson y necrólisis epidérmica tóxica).

- El LUMIRACOXIB también se retira en 2007 por reacciones hepáticas.

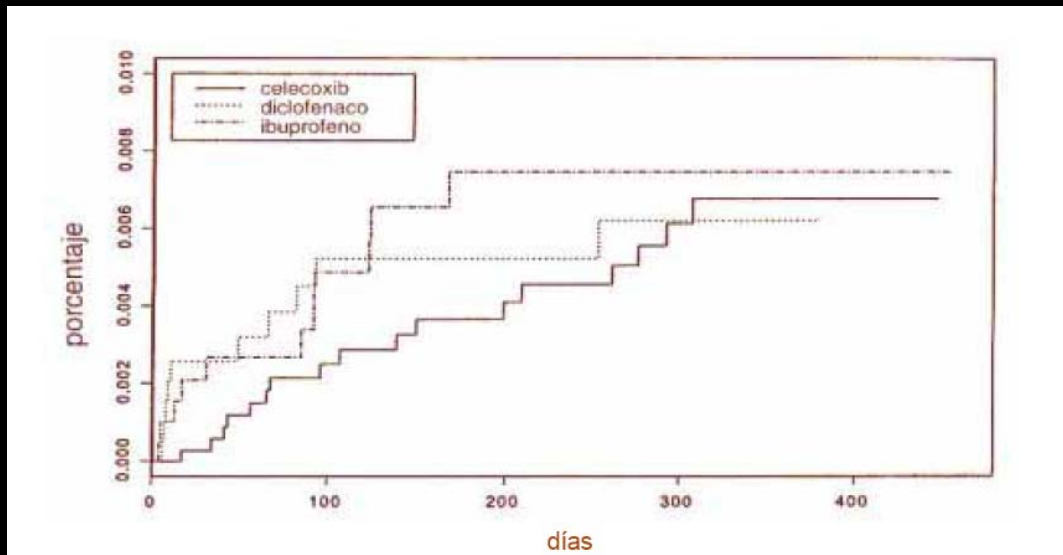
# CELECOXIB

2000

Se publican los resultados del estudio CLASS que mostraban a los 6 meses de seguimiento menos úlceras sintomáticas

pero no comunicaron los resultados a los 12 meses (como estaba en protocolo) que no mostraron diferencias.

Hrachover et al. JAMA 2001; 286:2398.



# CELECOXIB

2009

Un prominente investigador del celecoxib admite haberse inventado los datos de 21 artículos en dolor postoperatorio.

Anesthesiology 2009; 110:1-1.

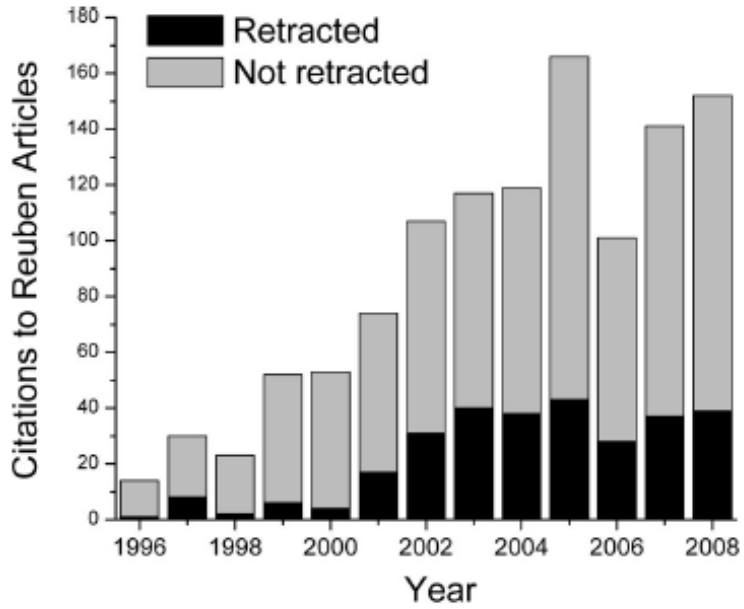
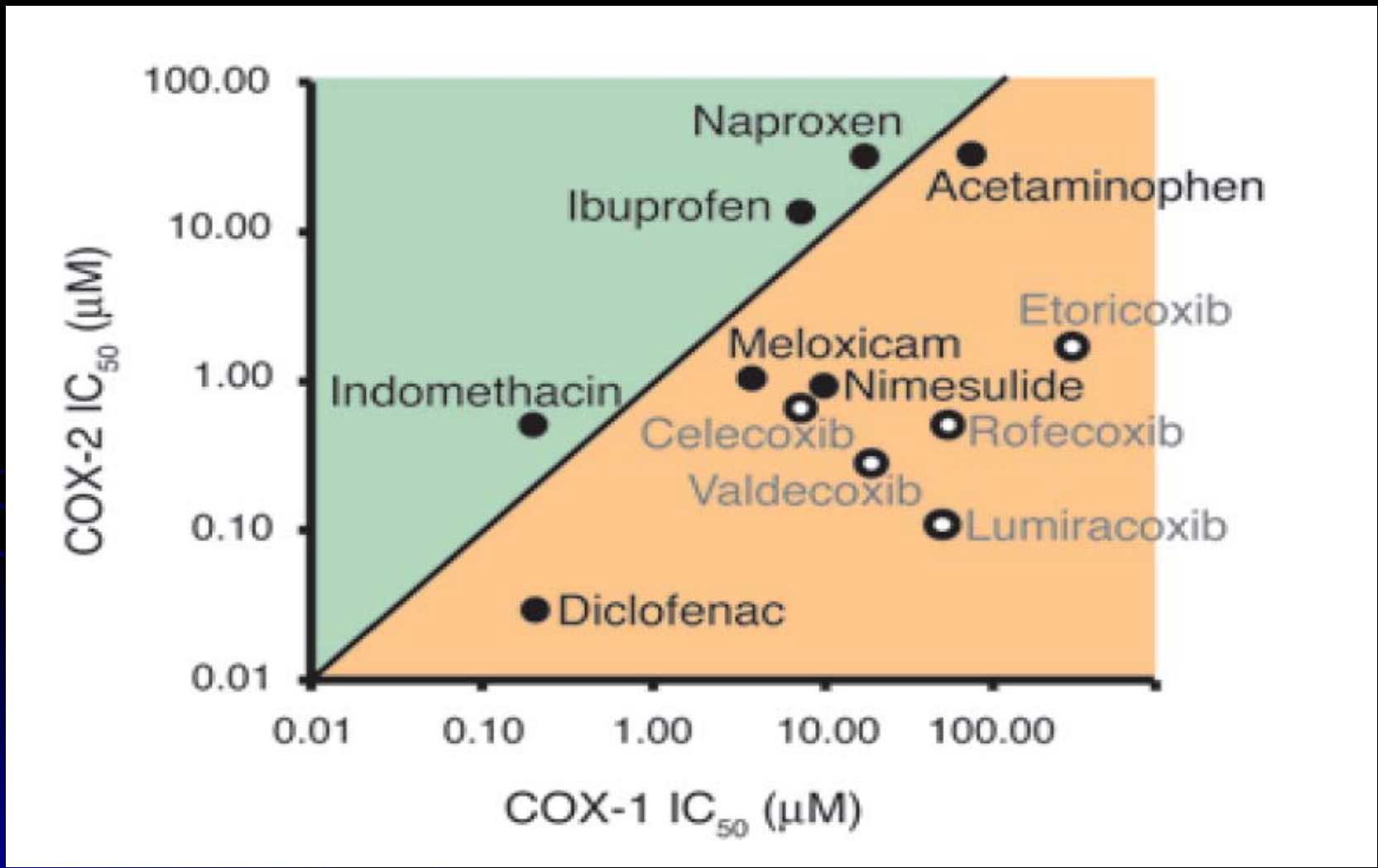



Fig. 1. Total citations per year from published articles by S. S. Reuben that are now retracted and those that have not been retracted. Source: ISI Web of Knowledge. Philadelphia, Thomson Reuters. Available at: http://www.isiwebofknowledge.com/. Accessed February 2, 2009.

- ROFECOXIB
- CELECOXIB
- VALDECOXIB
- LUMIRACOXIB
- ETORICOXIB

# Los coxib no son los únicos AINE selectivos de la COX-2



# Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation

Y-F Chen,[1*] P Jobanputra,[2] P Barton,[3] S Bryan,[3] A Fry-Smith,[1] G Harris[4] and RS Taylor[5]

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[2] Department of Rheumatology, University Hospital Birmingham NHS Trust, Selly Oak Hospital, UK
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* Corresponding author

## *Executive summary*

*Health Technology Assessment* 2008; Vol. 12: No. 11



## Per capita spending in Canada: $11.90

### Drugs in this therapeutic category

- Cyclooxgenase-2 (COX-2) inhibitors brand (e.g. celecoxib)
- COX-2 inhibitors generic (diclofenac, etodolac, meloxicam)
- Older NSAIDS (e.g. naproxen)

### Common goal of therapy

- Reduce symptoms of pain or inflammation

### Examples of indicated conditions

- Osteoarthritis
- Rheumatoid arthritis

# EFICACIA

- Los coxibs han demostrado una eficacia equivalente al resto de AINE.

# SEGURIDAD GASTROINTESTINAL

**CELECOXIB**

- Se asoció a menos eventos clínicos gastrointestinales que otros AINE en estudios a corto plazo (hasta 6 meses).
- A más largo plazo (12 meses) no se encontraron diferencias.

# SEGURIDAD GASTROINTESTINAL

**ETORICOXIB**

- Se asoció menos eventos gastrointestinales que otros AINE.
- No se han encontrado diferencias en complicaciones.

# SEGURIDAD GASTROINTESTINAL

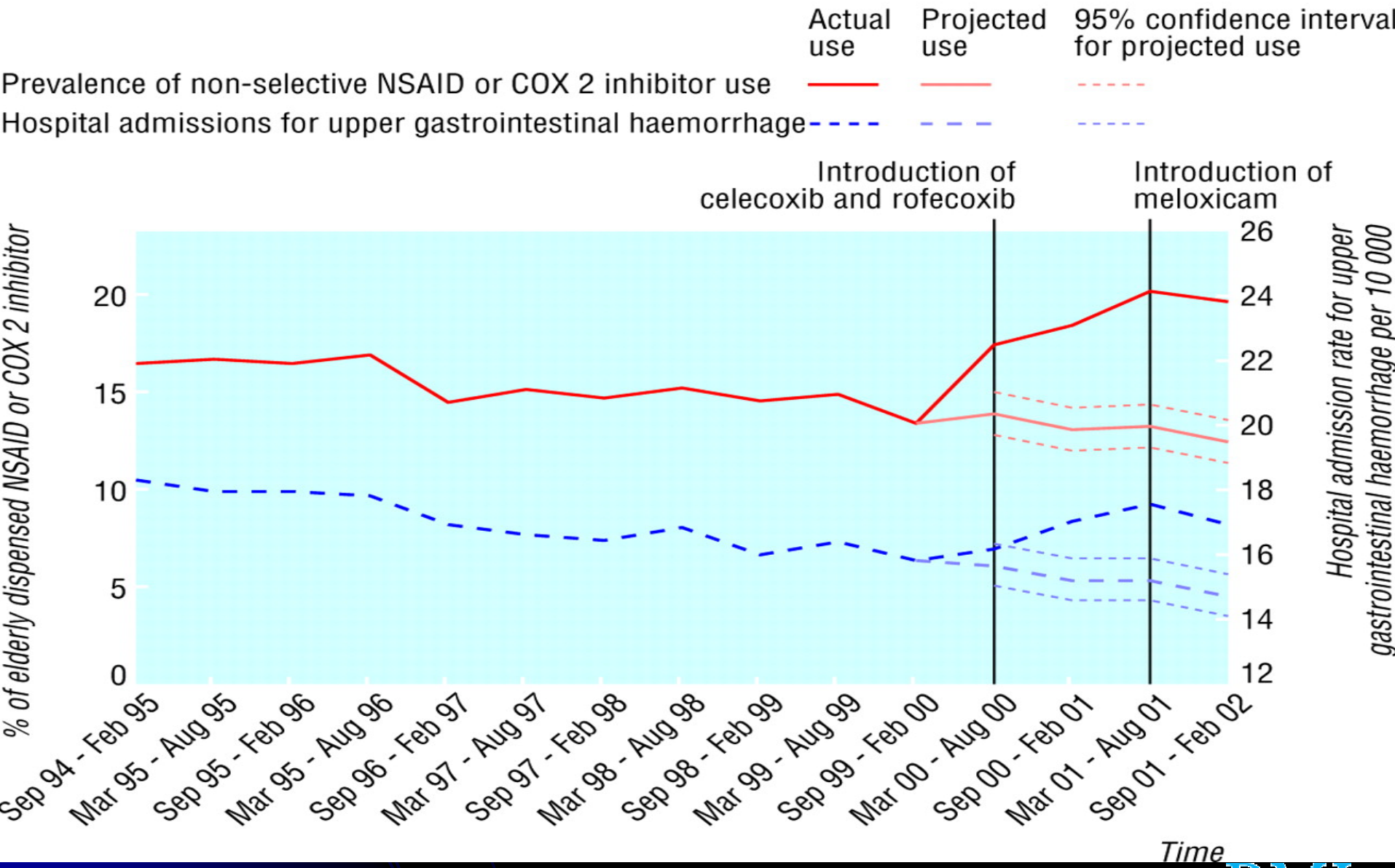
- Los coxibs son también causa de efectos gastrointestinales graves. Están contraindicados en úlcera o sangrado GI activos.

5% de sangrados en 6 meses en pacientes con antecedentes (Chan. 2002).

# SEGURIDAD GASTROINTESTINAL

No hay evidencia de que prescribir un coxib + gastroprotector sea mejor que prescribir un AINE tradicional + gastroprotector

# Prevalencia de uso de AINE y tasas de hospitalización por hemorragia digestiva alta en ancianos de Ontario (Canadá)




Mamdani, M. et al. BMJ 2004;328:1415-1416

# SEGURIDAD CARDIOVASCULAR

Los coxibs están contraindicados en pacientes con:

- Cardiopatía isquémica
- Enfermedad cerebrovascular
- Insuficiencia cardiaca de grado II-IV
- Enfermedad arterial periférica
- Etoricoxib en hipertensión arterial no controlada

# COXIBS EN AP NAVARRA

*04/2008 a 03/2009*

| | |
|---|---|
| **PACIENTES CON COXIB** | 9307 |
| **Nº PACIENTES CON COXIB CON CONTRAINDICACIÓN POR PATOLOGÍA CARDIOVACULAR** | 1143 |
| **% PACIENTES CON COXIB CON CONTRAINDICACIÓN POR PATOLOGÍA CARDIOVACULAR** | 12% |

# SEGURIDAD CARDIOVASCULAR

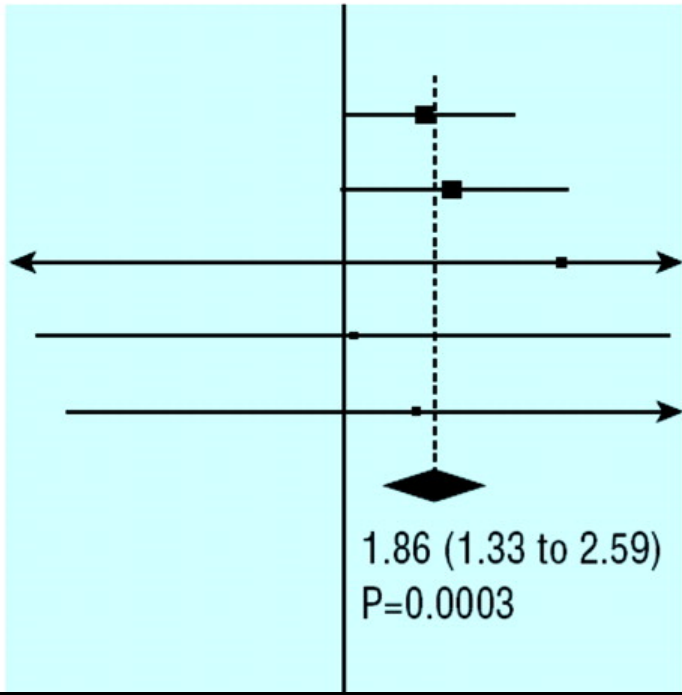
## COXIBS

- Presentan un mayor riesgo aterotrombótico; especialmente de infarto de miocardio respecto a los pacientes no tratados.
- El riesgo aproximadamente se dobla respecto a no usarlos
- En población general hablamos de 3 episodios extra por cada 1000 pacientes/año.
- Presentan un riesgo cardiovascular mayor que otros AINE (naproxeno, ibuprofeno ≤1.200mg/d)
- El diclofenaco parece tener un riesgo cardiovascular similar.

# Efectos de los coxibs en el infarto de miocardio

| COX 2 inhibitor | No of trials | Events/person years: Allocated COX 2 inhibitor | Events/person years: Allocated placebo | Rate ratio: COX 2 inhibitor: placebo |
|---|---|---|---|---|
| **Myocardial infarction** | | | | |
| Rofecoxib | 37 | 54/6638 | 30/6415 | |
| Celecoxib | 41 | 44/8976 | 9/4953 | |
| Etoricoxib | 17 | 2/753 | 0/414 | |
| Lumiracoxib | 12 | 5/1375 | 2/584 | |
| Valdecoxib | 14 | 8/748 | 1/273 | |
| Subtotal | 121 | 113/18 490 (0.6%/year) | 42/12 639 (0.3%/year) | 1.86 (1.33 to 2.59) P=0.0003 |

Heterogeneity between five drugs: $\chi^2$=1.0, df=4, P=0.9



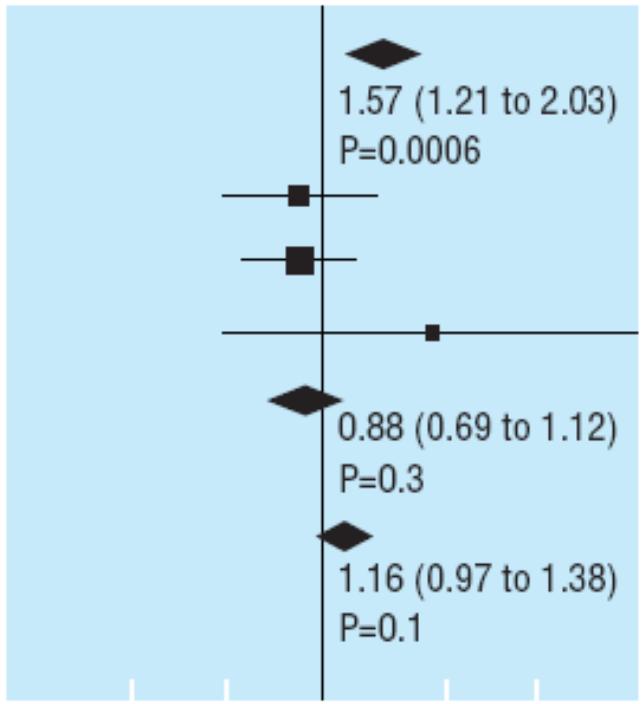
Antman, E. M. et al. Circulation 2007;115:1634-1642

Circulation

| COX 2 inhibitor versus: | No of trials | Events/person years: Allocated COX 2 inhibitor | Events/person years: Allocated NSAID | Rate ratio: COX 2 inhibitor: NSAID |
|---|---|---|---|---|
| **Vascular events** | | | | |
| (a) Naproxen | 42 | 185/16 360 (1.1%/year) | 81/10 978 (0.7%/year) | 1.57 (1.21 to 2.03) P=0.0006 |
| Ibuprofen | 24 | 46/5848 | 47/5160 | |
| Diclofenac | 26 | 101/10 886 | 79/6913 | |
| Other non-naproxen | 7 | 8/166 | 4/274 | |
| (b) Any non-naproxen | 51 | 155/16 900 (0.9%/year) | 130/12 347 (1.1%/year) | 0.88 (0.69 to 1.12) P=0.3 |
| Any NSAID | 91 | 340/33 260 (1.0%/year) | 211/23 325 (0.9%/year) | 1.16 (0.97 to 1.38) P=0.1 |

Heterogeneity between (a) and (b): $\chi^2$=10.2, df=1, P=0.001

Between non-naproxen NSAIDs: $\chi^2$=2.6, df=2, P=0.3

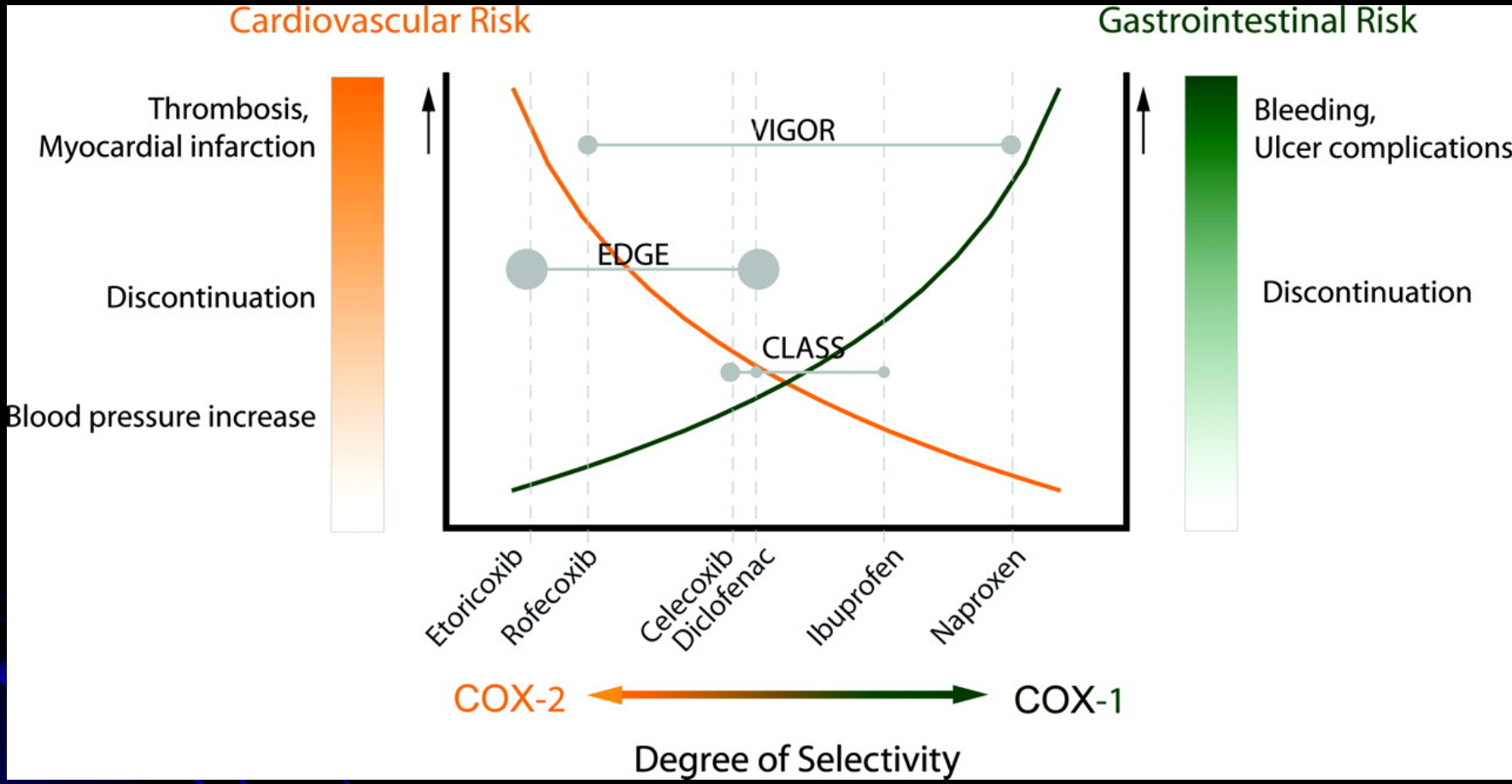


# Asociación con AAS

- En prevención secundaria CV un coxib está contraindicado.
- No se ha demostrado que la asociación de un inhibidor selectivo de la COX-2 y el ácido acetilsalicílico a dosis bajas, tenga un menor riesgo gastrointestinal que la asociación de este último antiagregante con AINE tradicionales

**¿Está el coxib indicado en alguien?**

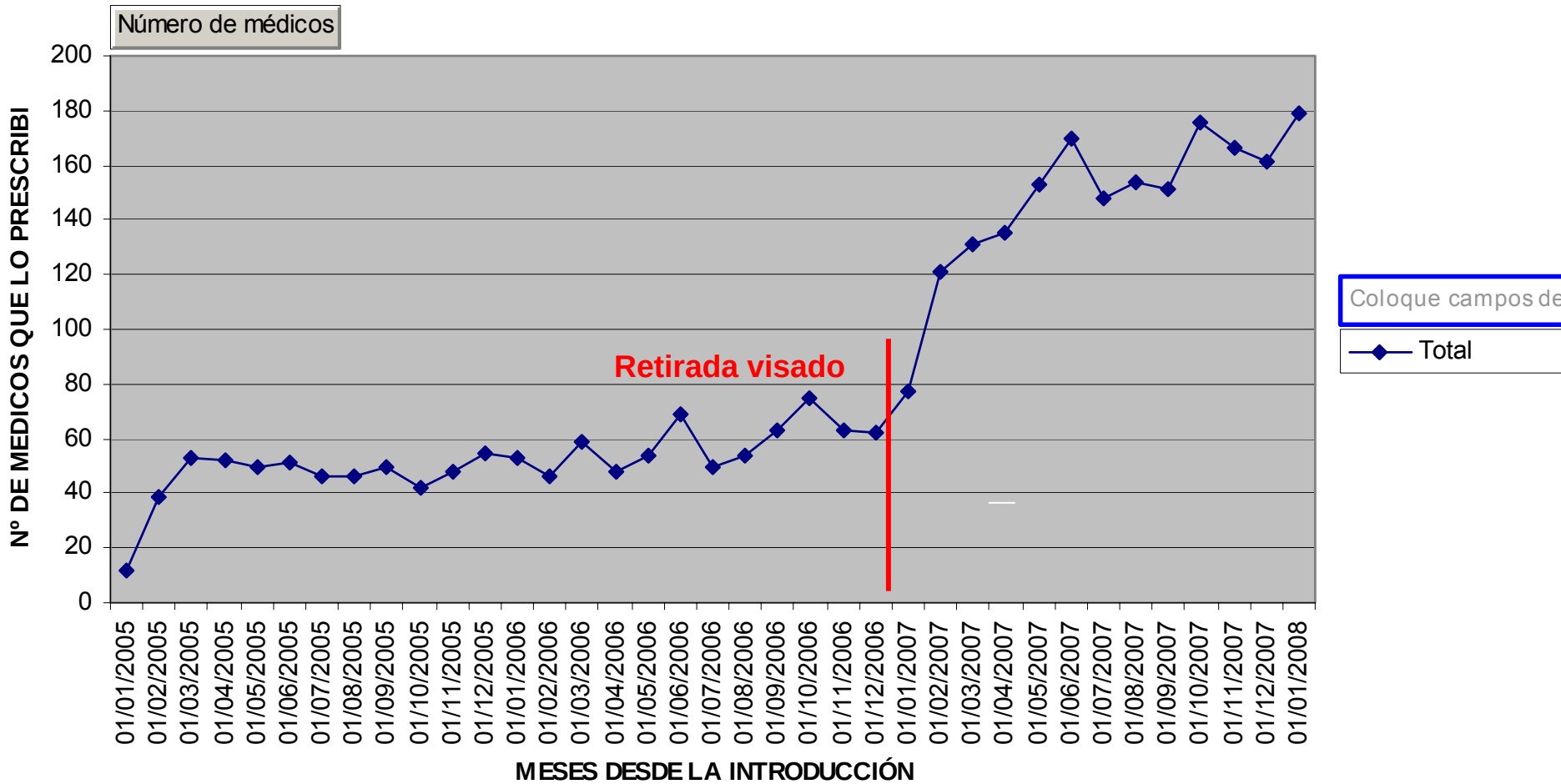
# IMPLICACIÓN DE LA SELECTIVIDAD HACIA LA COX EN LA SEGURIDAD DE LOS AINE




Antman, E. M. et al. Circulation 2007;115:1634-1642

Principio activo ETORICOXIB

## DIFUSIÓN DE NUEVOS FÁRMACOS ENTRE LOS MÉDICOS




Fecha

# Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis

Matthew C. Becker, MD,[a] Thomas H. Wang, MD,[a] Lisa Wisniewski, RN,[a] Kathy Wolski, MPH,[a] Peter Libby, MD,[b] Thomas F. Lüscher, MD,[c] Jeffrey S. Borer, MD,[d] Alice M. Mascette, MD,[e] M. Elaine Husni, MD, MPH,[f] Daniel H. Solomon, MD, MPH,[g] David Y. Graham, MD,[h] Neville D. Yeomans, MD,[i] Henry Krum, MBBS, PhD, FRACP,[j] Frank Ruschitzka, MD,[c] A. Michael Lincoff, MD,[a] and Steven E. Nissen, MD[a] for the PRECISION Investigators

*Cleveland, OH; Boston, MA; Zurich, Switzerland; New York, NY; Bethesda, MD; Houston, TX; and Sydney and Melbourne, Australia*

**Background** Pain management in patients with osteoarthritis or rheumatoid arthritis often requires long-term use of nonsteroidal antiinflammatory drugs (NSAIDs). However, the relative cardiovascular safety of these therapies remains uncertain.

**Methods** The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial will evaluate the cardiovascular safety of celecoxib, ibuprofen, and naproxen. Approximately 20,000 patients with symptomatic osteoarthritis or rheumatoid arthritis at high risk for, or with, established cardiovascular disease will be randomized in this double-blind, triple dummy, multinational, multicenter study. The primary end point is the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The trial will continue until 762 primary events occur with at least 18 months follow-up. Noninferiority of any of the regimens will require a 97.5% upper CI of the hazard ratio (HR) $\leq$1.33 and point estimate $\leq$1.12 for both intent-to-treat (ITT) and modified ITT populations.

**Conclusion** PRECISION, the first study of patients with high cardiovascular risk chronically treated with a cyclooxygenase-2 selective inhibitor or nonselective NSAID, will define the relative cardiovascular safety profile of celecoxib, ibuprofen, and naproxen and provide data to help guide NSAID use for pain management for this population. (Am Heart J 2009;157:606-12.)

# CONCLUSIONES

- Los coxibs son igualmente eficaces que otros AINE para el control de síntomas
- No hay evidencia de que los coxibs sean más seguros que otros AINE usados con gastroprotección
- Los coxibs tienen mayor riesgo cardiovascular que otros AINE

# Para saber más

- Use of Nonsteroidal Antiinflammatory Drugs: an Update for Clinicians. A Scientific Statement From the American Heart Association.
  http://circ.ahajournals.org/cgi/content/full/115/12/1634
- Public CHMP assessment report for medicinal products containing non-selective non steroidal antiinflammatorydrugs (NSAIDs).
  http://www.emea.europa.eu/pdfs/human/opiniongen/44213006en.pdf
- Antiinflamatorios no esteroideos y riesgo cardiovascular.
  http://www.cfnavarra.es/WebGN/SOU/publicac/BJ/textos/Bit_v16n5.pdf
- Comparative Effectiveness and Safety of Analgesics for Osteoarthritis.
  http://effectivehealthcare.ahrq.gov/repFiles/AnalgesicsExecSum.pdf
- Cardiovascular and gastrointestinal safety of NSAIDs.
  http://www.npc.co.uk/ebt/merec/cardio/cdrisk/resources/merec_extra_no30.pdf
- Update on the prescribing of NSAIDs.
  http://www.npc.co.uk/ebt/merec/pain/musculo/resources/merec_monthly_no02.pdf
- Drug Class Review on Cyclo-oxygenase (COX)-2 Inhibitors and Non-steroidal Anti-inflammatory Drugs (NSAIDs)

  http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=nsaids