Sistema Socio Sanitario

Ospedale Niguarda

Regione Lombardia

Quale Fans per cardiologo

Francesco Scaglione, MD, PhD

Postgraduate School of clinical pharmacology
University of Milan

Clinical Pharmacology Unit
Niguarda Ca' Granda- Hospital Milan
Italy

Ogni giorno
in Europa e negli Stati Uniti più di 30 milioni di persone assumono un FANS

[Friedewald VE et al. Am J Cardiol 2010;106:873–84].

A large meta-analysis of over 600 randomised trials showed that COX 2 inhibitors and high doses of traditional NSAIDs (that is, diclofenac, ibuprofen, and naproxen) increased the risk of hospital admission for heart failure from 1.9-fold to 2.5-fold compared with

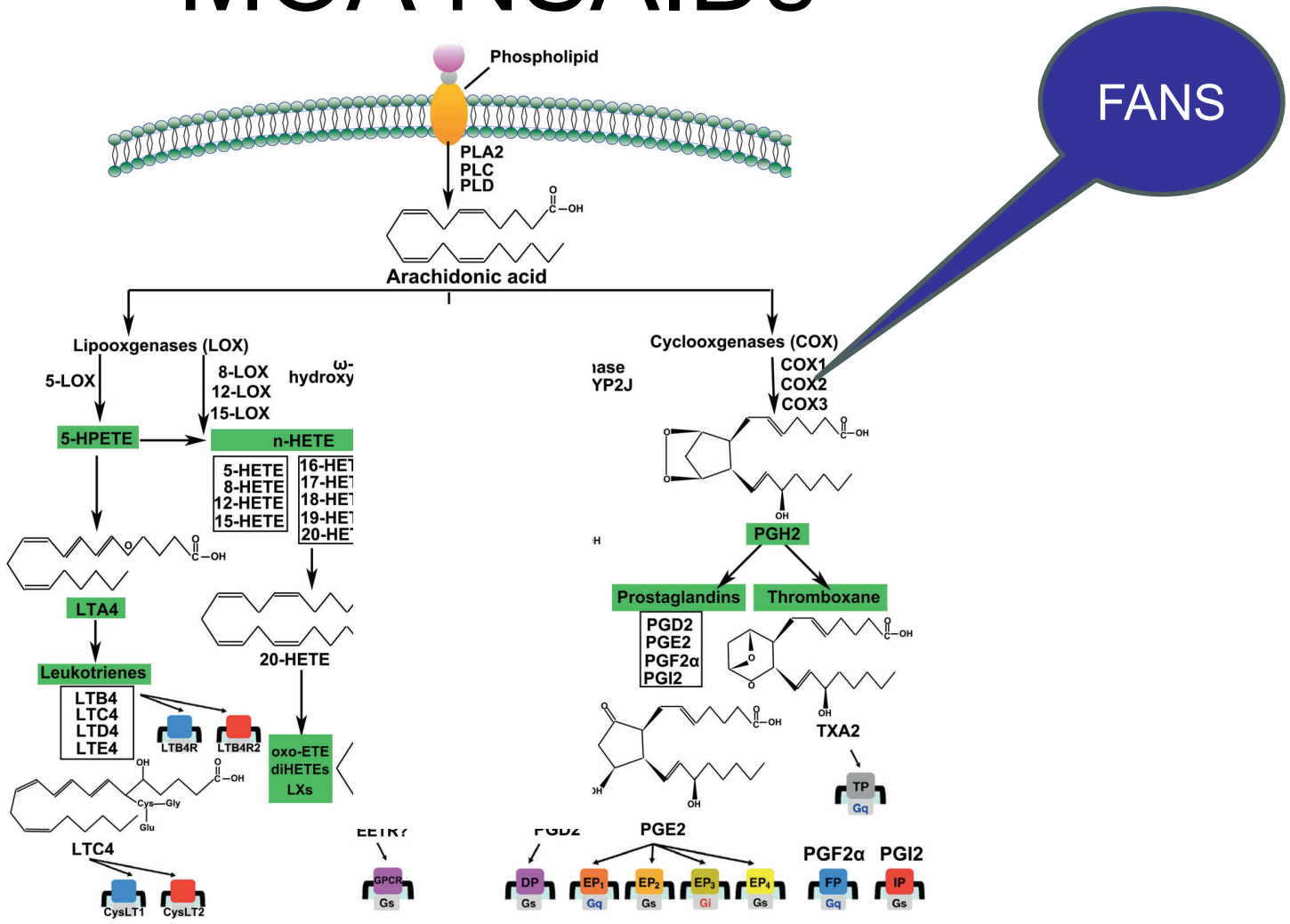
Bhala N, Emberson J, Merhi A, et al. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769-79.

FARMACI ANTINFIAMMATORI NON STEROIDEI (FANS)

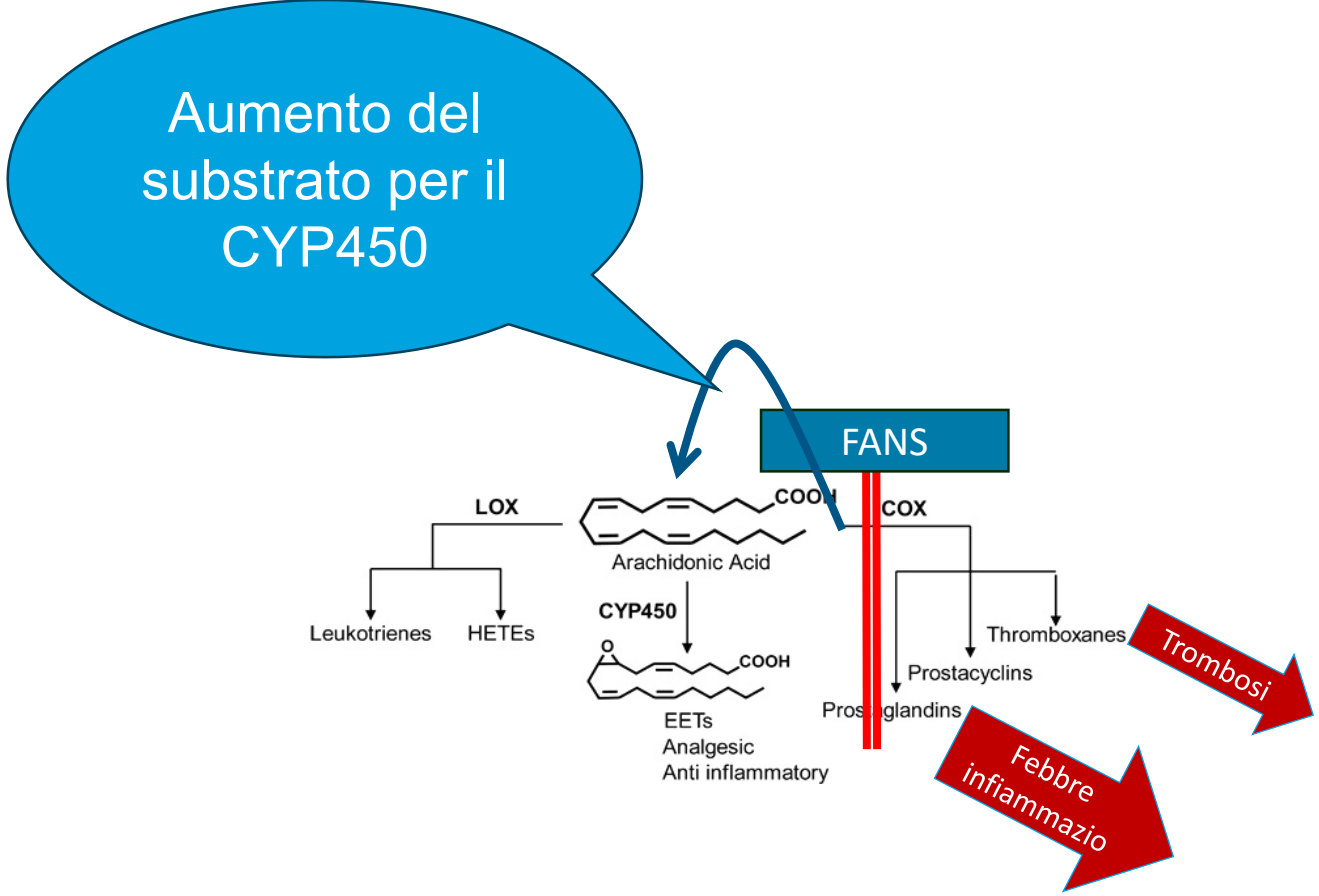
Azione antipiretica
Azione analgesica
Azione antinfiammatoria
Azione antiaggregante piastrinica

- **Come antipiretici**
- **Come analgesici**
- **Artrite reumatoide, artrite giovanile, spondilite anchilosante, osteoartrite**
- **Trattamento o profilassi malattie caratterizzate da iperaggregabilità delle piastrine**

MOA NSAIDs



Signal Transduction and Targeted Therapy (2021) 6:94



EET= epossieicosatrienoici

Signal Transduction and Targeted Therapy (2021) 6:94

Isoforme della PGH sintasi (COX)

COX-1

- Presente in forma costitutiva in quasi tutti i tessuti (es. piastrine, cellule endoteliali, tratto G.I., rene)

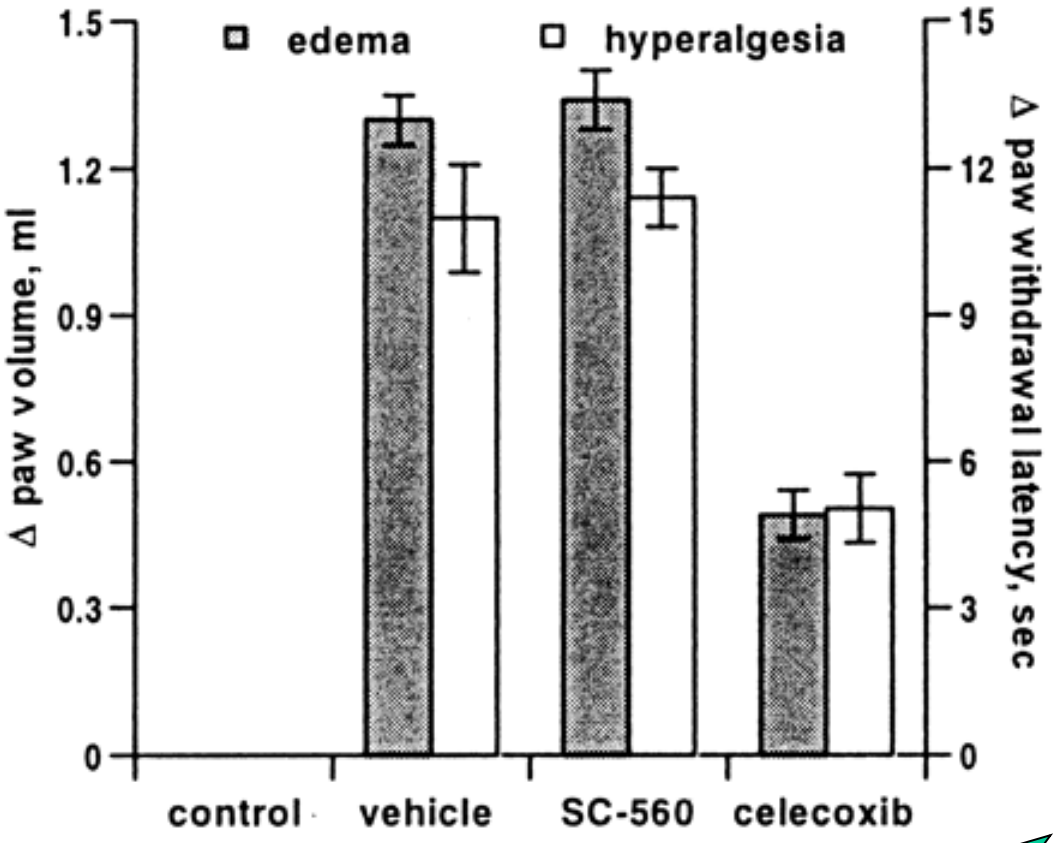
- Ruolo:

  Regolazione di funzioni omeostatiche (es. integrità mucosa gastrica, funzionalità piastrinica, flusso ematico renale)

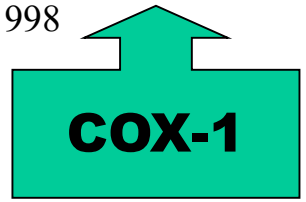
COX-2

- Presente in forma costitutiva solo in alcuni tessuti (es. cervello, rene, testicoli, prostata, ovaio)

- L'espressione è rapidamente indotta in risposta a stimoli pro-infiammatori (citochine, endotossine, fattori di crescita, …) in monociti, macrofagi, sinoviociti, condrociti, cellule endoteliali …



PNAS Vol. 95, Issue 22, 13313-13318, October 27, 1998



NSAIDs action is COX2 dependent

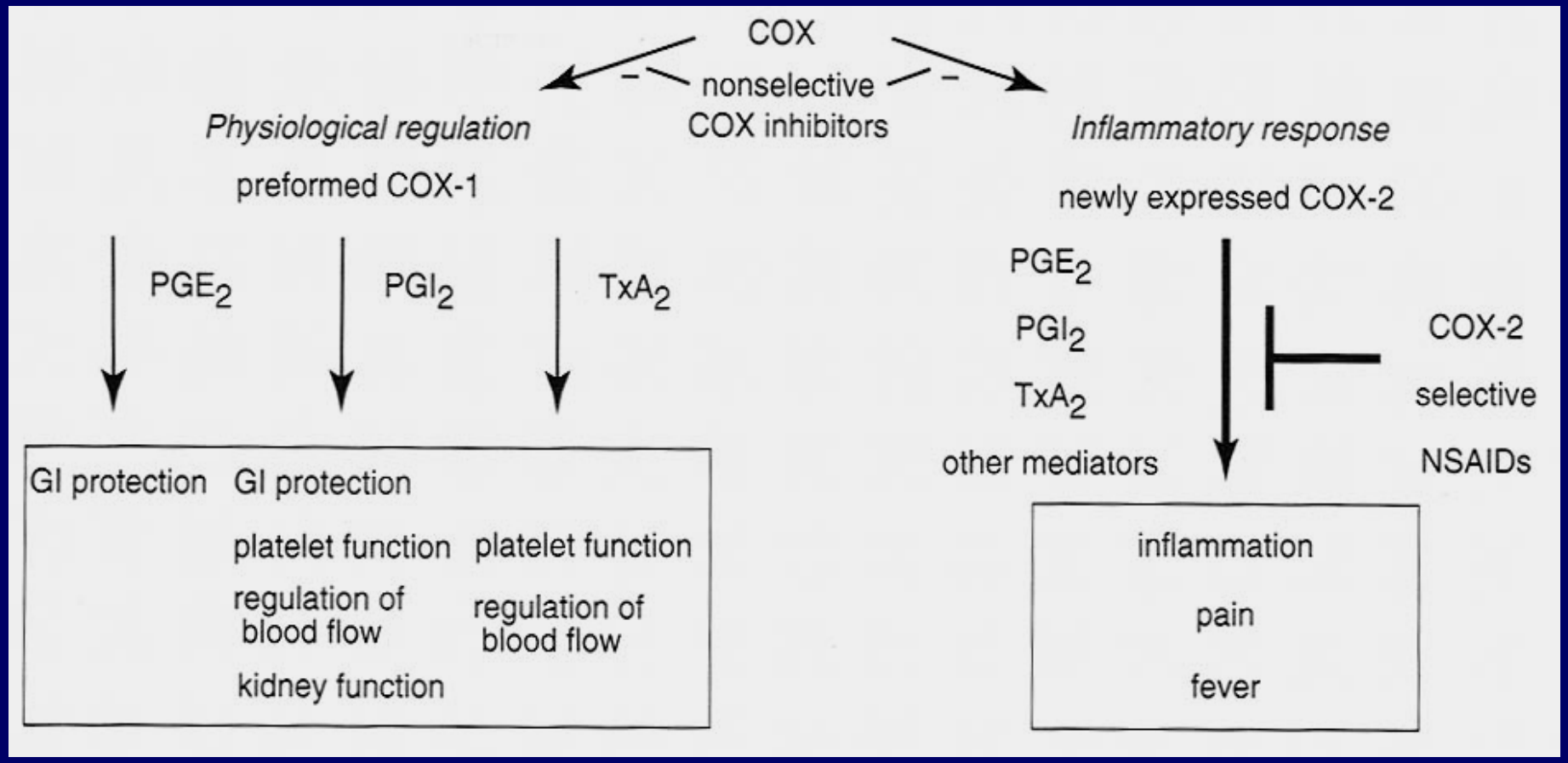
IC50 (μM) di FANS per COX-1 e COX-2

FANS	COX-2
ASA	13.88
Naproxene	28.19
Ibuprofene	24.3
Ketoprofene	0.88
Indometacina	0.44
Diclofenac	0.05
Nimesulide	0.56
Etoricoxib	1.1

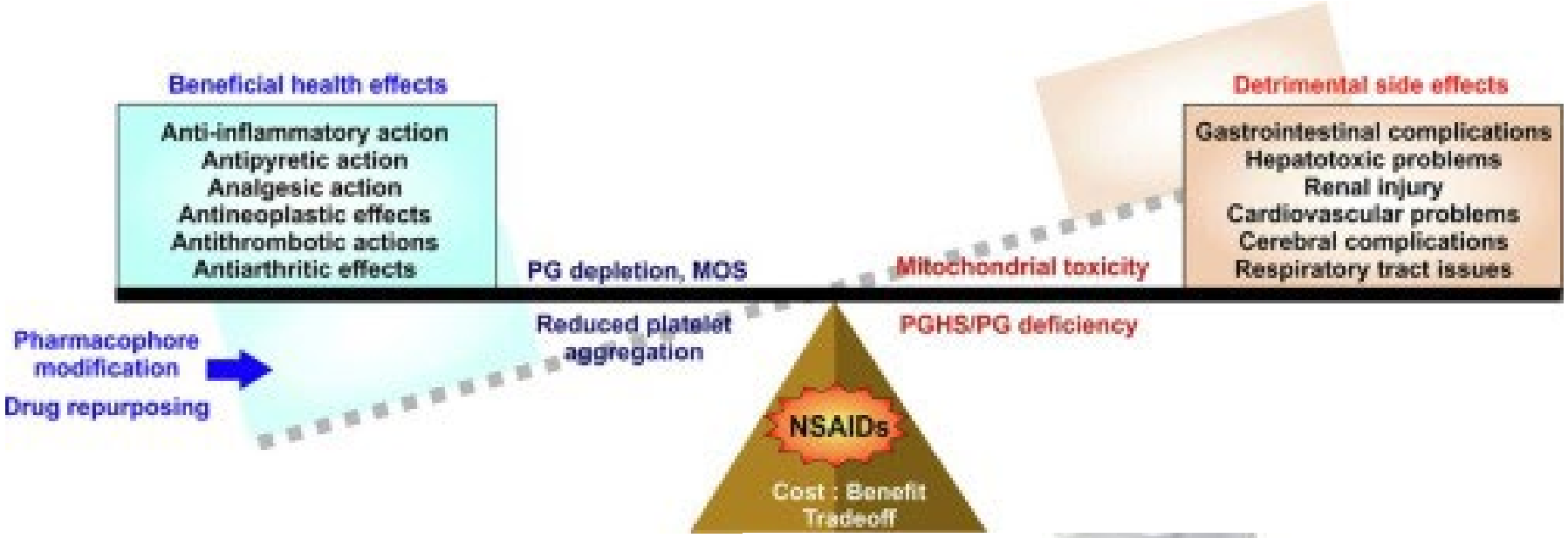
La Potenza diventa equivalente adattando la dose

Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. Am J Med. 1998 May;104(5):413-21.

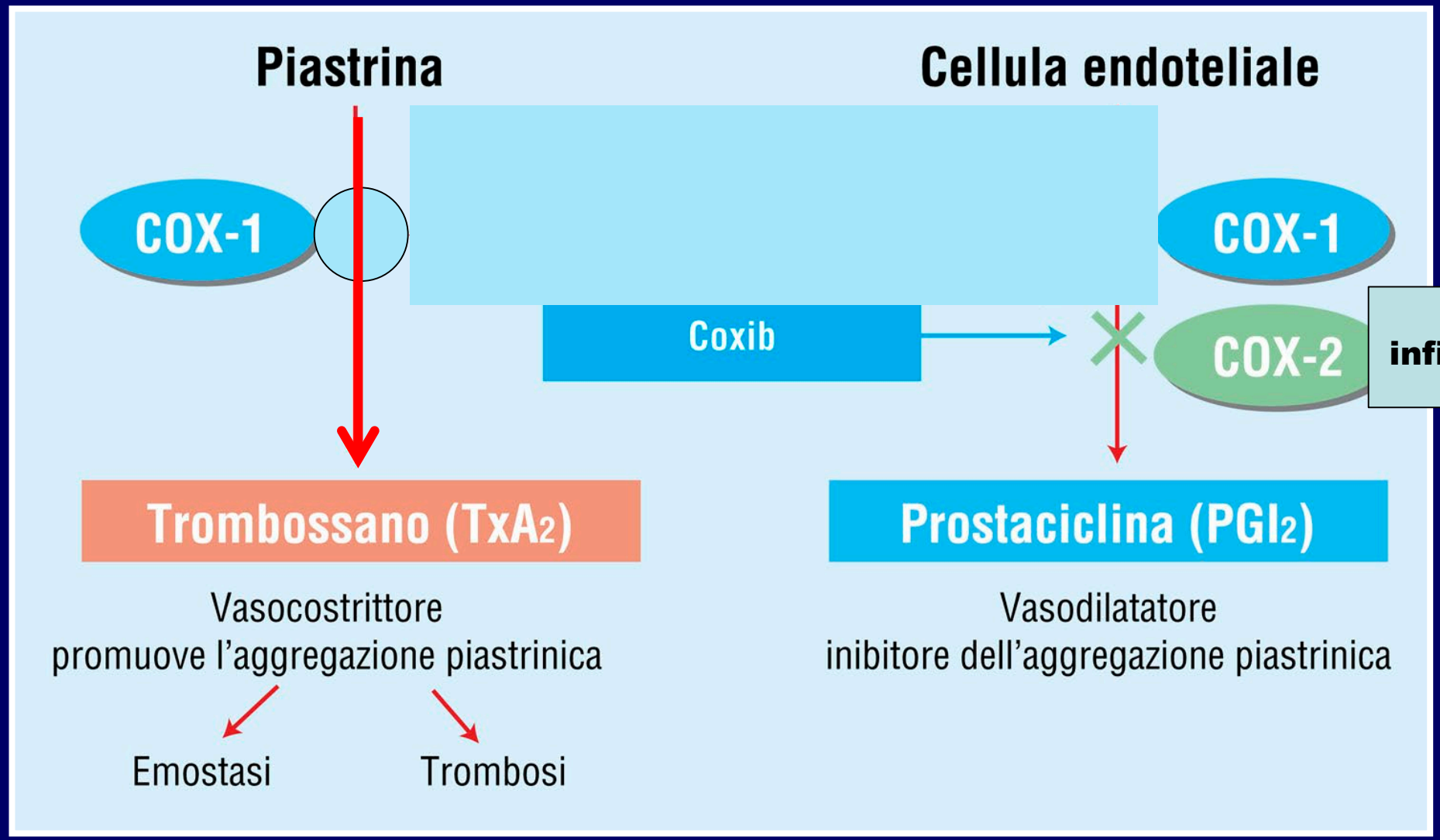
D. Riendeau et al., Etoricoxib (MK-0663): Preclinical Profile and Comparison with Other Agents That Selectively Inhibit Cyclooxygenase-2, JPET 296:558–566, 2001



L'inibizione della COX-2 riduce la biosintesi dei prostanoidi algogeni e flogogeni

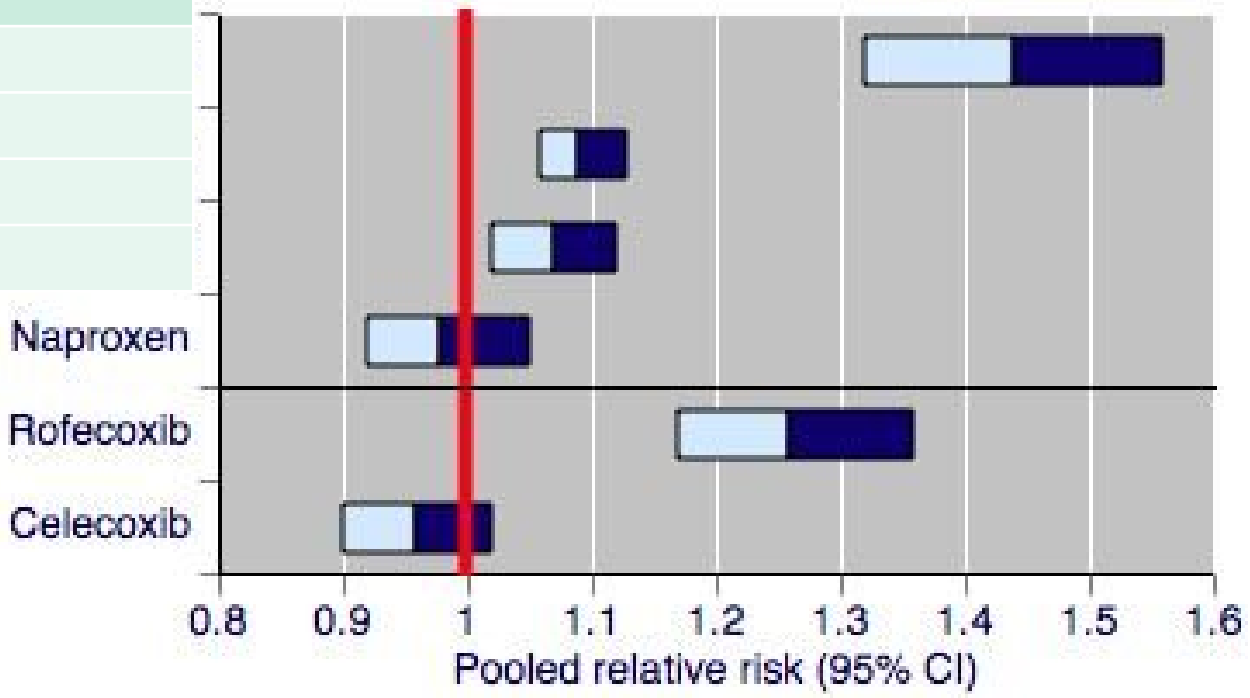

Beneficial health effects
Anti-inflammatory action
Antipyretic action
Analgesic action
Antineoplastic effects
Antithrombotic actions
Antiarthritic effects
PG depletion, MOS
Mitochondrial toxicity
Detrimental side effects
Gastrointestinal complications
Hepatotoxic problems
Renal injury
Cardiovascular problems
Cerebral complications
Respiratory tract issues
Pharmacophore modification
Drug repurposing
Reduced platelet aggregation
PGHS/PG deficiency
NSAIDs
Cost : Benefit Tradeoff

Effetti cardiovascolari dei FANS e dei coxib.



FANS	COX-2	COX-1
ASA	13.88	4.45
Naproxene	28.19	32.01
Ibuprofene	24.3	4.8
Ketoprofene	0.88	0.11
Indometacina	0.44	0.19
Diclofenac	0.05	0.15
Nimesulide	0.56	4.1
Etoricoxib	1.1	116

ANS e rischio di Infarto del Miocardio Acuto



S Hernández-Díaz et al. Non-steroidal anti-inflammatory drugs and risk of acute myocardial infarction. Basic & Clinical Pharmacology & Toxicology . 2006 98: 266-274

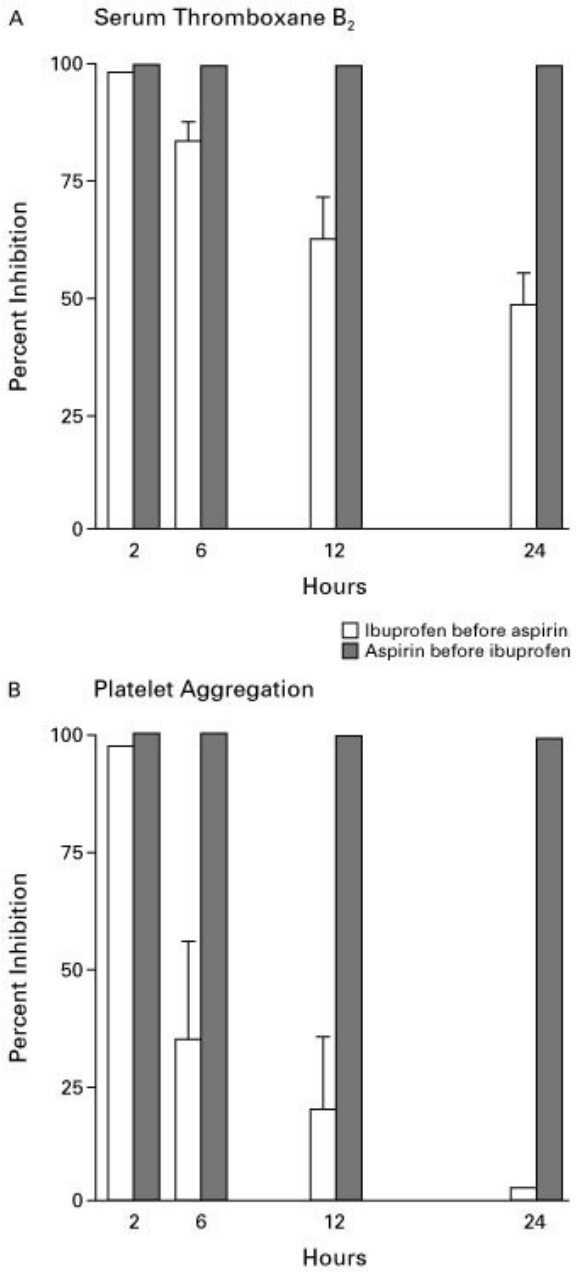
Effetto avverso (ma anche terapeutico)

INIBIZIONE DELL'AGGREGAZIONE PIASTRINICA

E' dovuta al blocco della sintesi di endoperossidi ciclici e trombossani (vasocostrittori e proaggreganti) a livello piastrinico.

NON TUTTI I FANS HANNO QUESTO EFFETTO allo stesso modo

L'aspirina (efficace già a 80 mg) agisce inattivando in modo irreversibile la cicloossigenasi piastrinica; l'effetto di una singola dose può durare fino a 8-10 giorni, fino a quando cioè non si rendano disponibili nuove piastrine. Questo è il motivo per cui l'aspirina è l'unico dei FANS utilizzato come antiaggregante nelle malattie tromboemboliche.

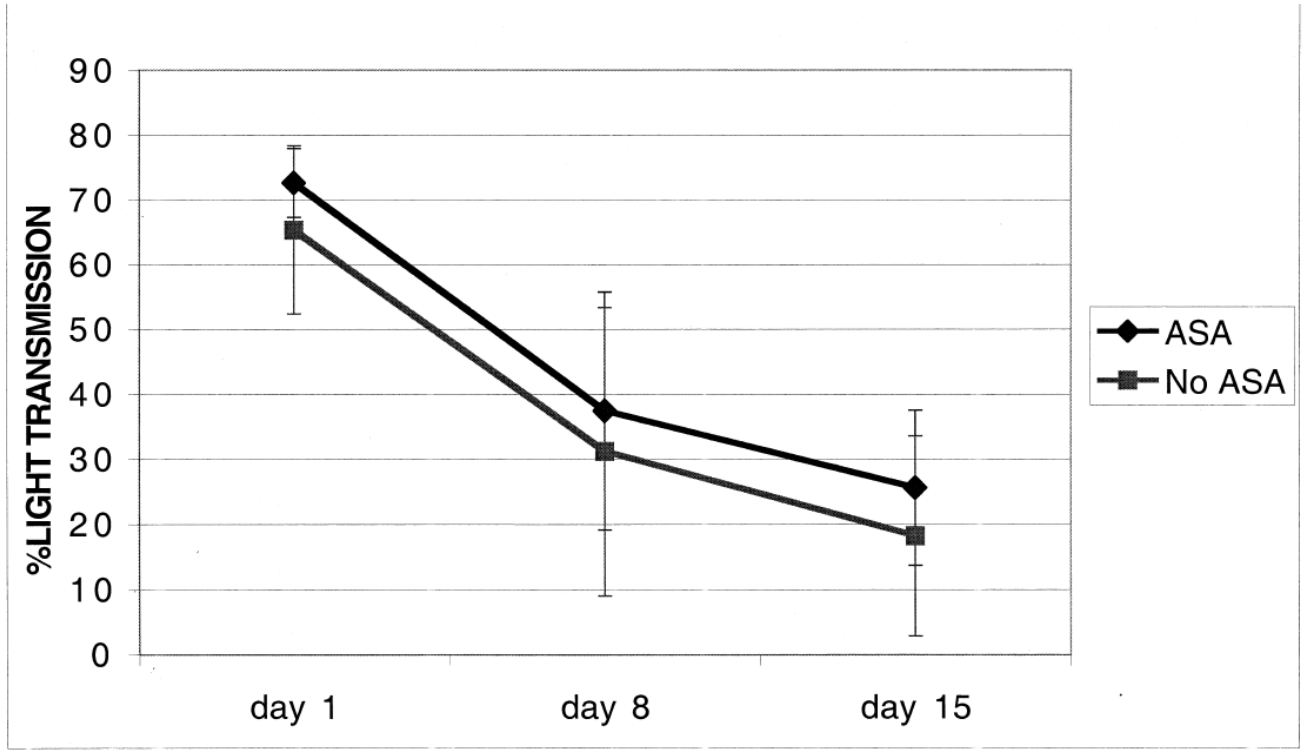


The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2001;345:1809-1817

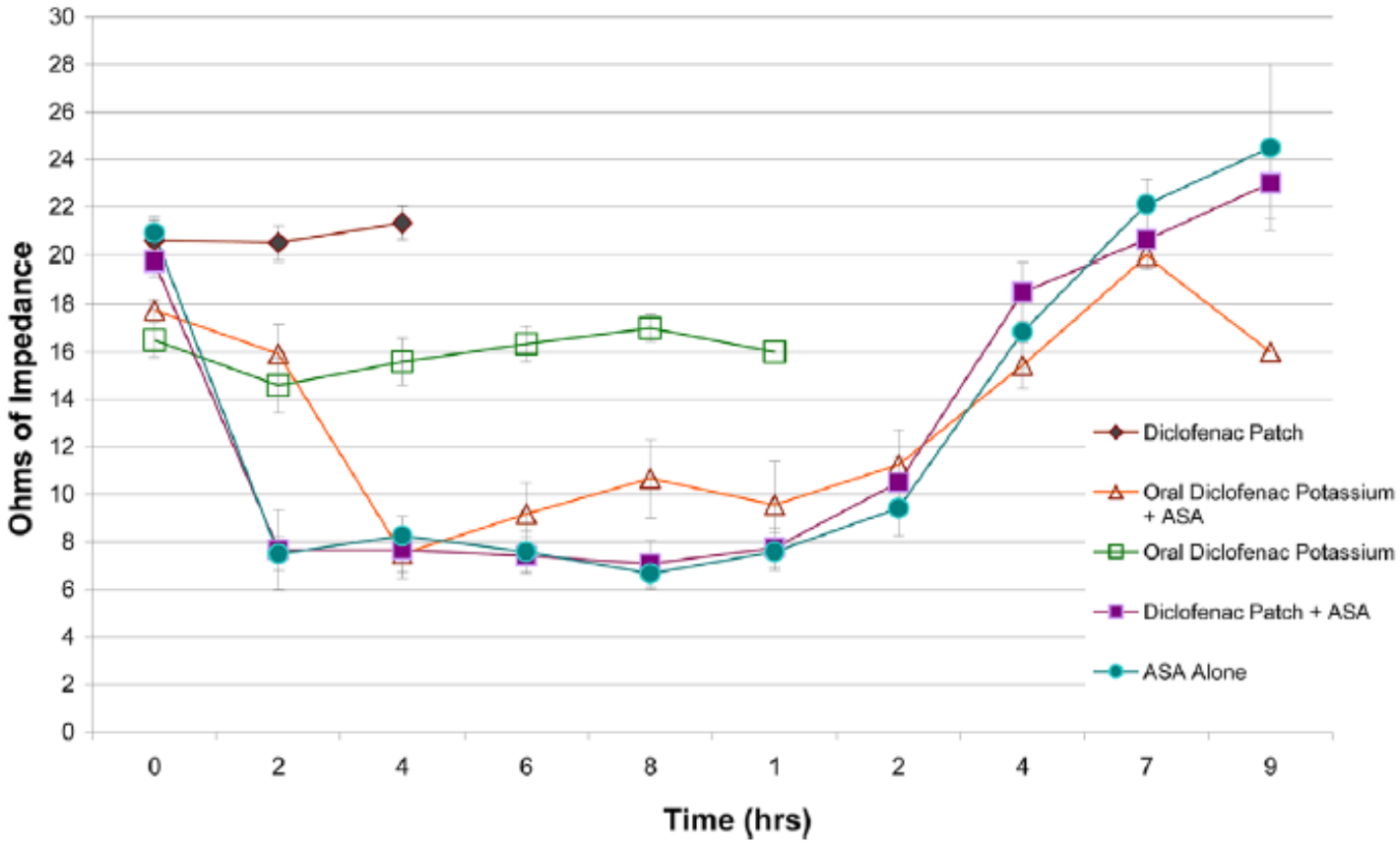
Mean Inhibition of Platelet Cyclooxygenase-1 Activity, as Assessed by Measurement of Serum Thromboxane B_2 (Panel A) and Inhibition of Platelet Aggregation (Panel B) in Subjects Taking Ibuprofen before Aspirin or Aspirin before Ibuprofen

Aggregazione piastrinica in risposta all'acido arachidonico .
Il gruppo che ha ricevuto l'aspirina (**ASA)** dai giorni 8 a 14 era statisticamente indistinguibile dal gruppo che ha ricevuto **ketoprofene** da solo (senza ASA) dai giorni 8 a 14.



A

Van Solingen et al. Antiplatelet Effects of Aspirin and Ketoprofen. Am J Med. 2001;111:285–289.



2. Effects of oral and topical diclofenac on the antiplatelet effects of aspirin as determined by aggregation to collagen.

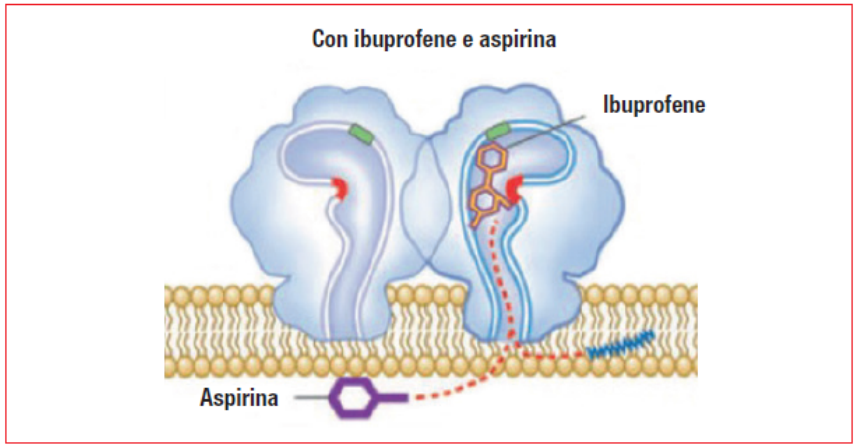
Rowcliffe et al. *The Journal of Clinical Pharmacology* / Vol 56 No 4 2016

FANS E ASPIRINA A BASSE DOSI

Ibuprofene si lega allo stesso binding site dell'aspirina

Perdita dell'attività antipiastrinica dell'aspirina e aumento del rischio aterotrombotico

L'ibuprofene previene l'accesso completo dell'aspirina all'interno della COX-1, impedendogli di acetilare e quindi inibire l'enzima (da Mackenzie et al., 2010, mod.) [9].



Oltre all' ibuprofene anche altri FANS come naproxene, nimesulide, oxaprozin, piroxicam e dipirone inibiscono l'azione dell'aspirina

ketoprofene si lega ad un binding site diverso da quello dell'aspirina all'interno dell'enzima COX

[CANCER RESEARCH 57, 2452–2459, June 15, 1997]

Apoptosis Primarily Accounts for the Growth-inhibitory Properties of Sulindac Metabolites and Involves a Mechanism That Is Independent of Cyclooxygenase Inhibition, Cell Cycle Arrest, and p53 Induction[1]

Gary A. Piazza,[2] Alanna K. Rahm, Tyler S. Finn, Benjamin H. Fryer, Han Li, Alan L. Stoumen, Rifat Pamukcu, and Dennis J. Ahnen

Cell Pathways, Inc., Denver, Colorado 80012-4526 [G. A. P., A. K. R., T. S. F., B. H. F., H. L., A. L. S., R. P.]; Department of Veterans Affairs Medical Center, and The University of Colorado, Denver, Colorado [D. J. A.]

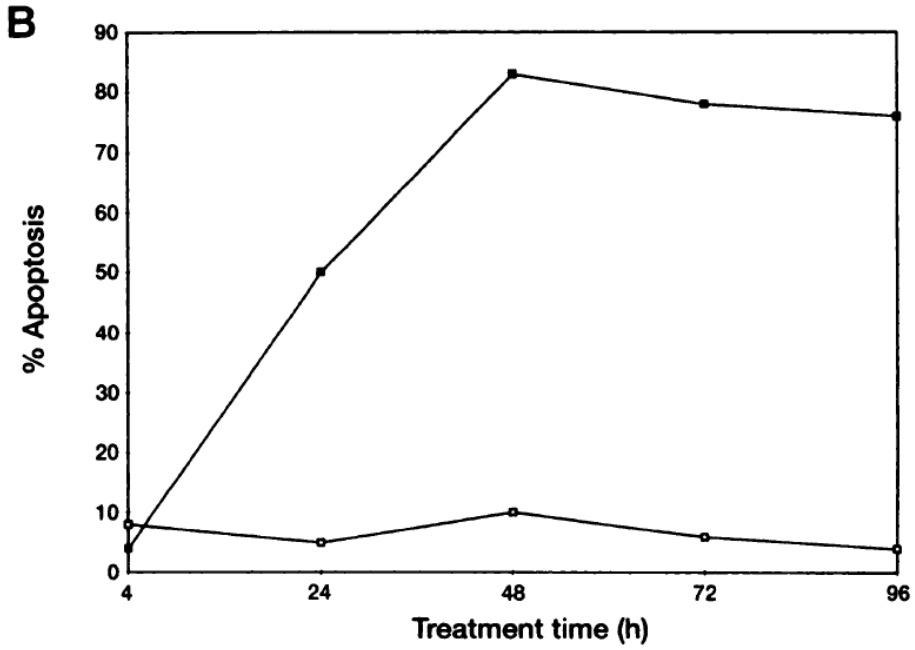


Fig. 1. Time course for growth inhibition (*A*) and apoptosis (*B*) of HT-29 cells after treatment with sulindac sulfide. HT-29 cells (4×10^6 cells) were established in 75-cm^2 flasks and allowed to growth for 3 days prior to treatment. Treatment was initiated at time 0 with either sulindac sulfide (final concentration, 120 μM; ■) or vehicle (0.1% DMSO; □), which was added with fresh medium. After the indicated time, the number of viable and apoptotic cells that were attached or floating was determined from the same flask as described in "Materials and Methods." The data shown are from one of three representative experiments. All data shown were collected from the same experiment.

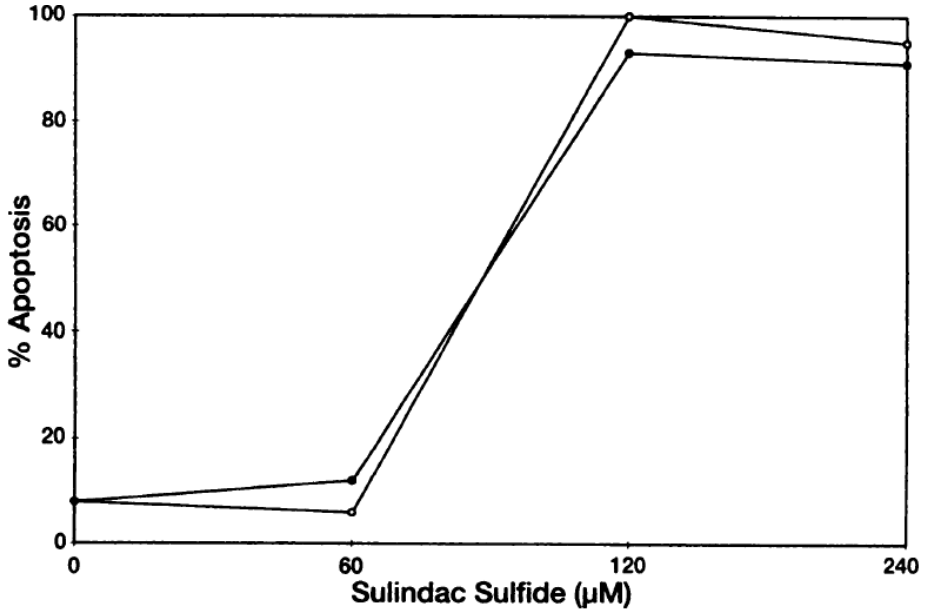


Fig. 3. Effect of dimethyl-PGE_2 on sulindac sulfide induction of apoptosis. HT-29 cells (1×10^6 cells) were plated in 25-cm^2 flasks, allowed to grow for 10 days, and treated with the indicated dose of sulindac sulfide in the presence (■) or absence (□) of dimethyl-PGE_2 (5 μM) for 6 days. Apoptosis was measured by morphology as described under "Materials and Methods."

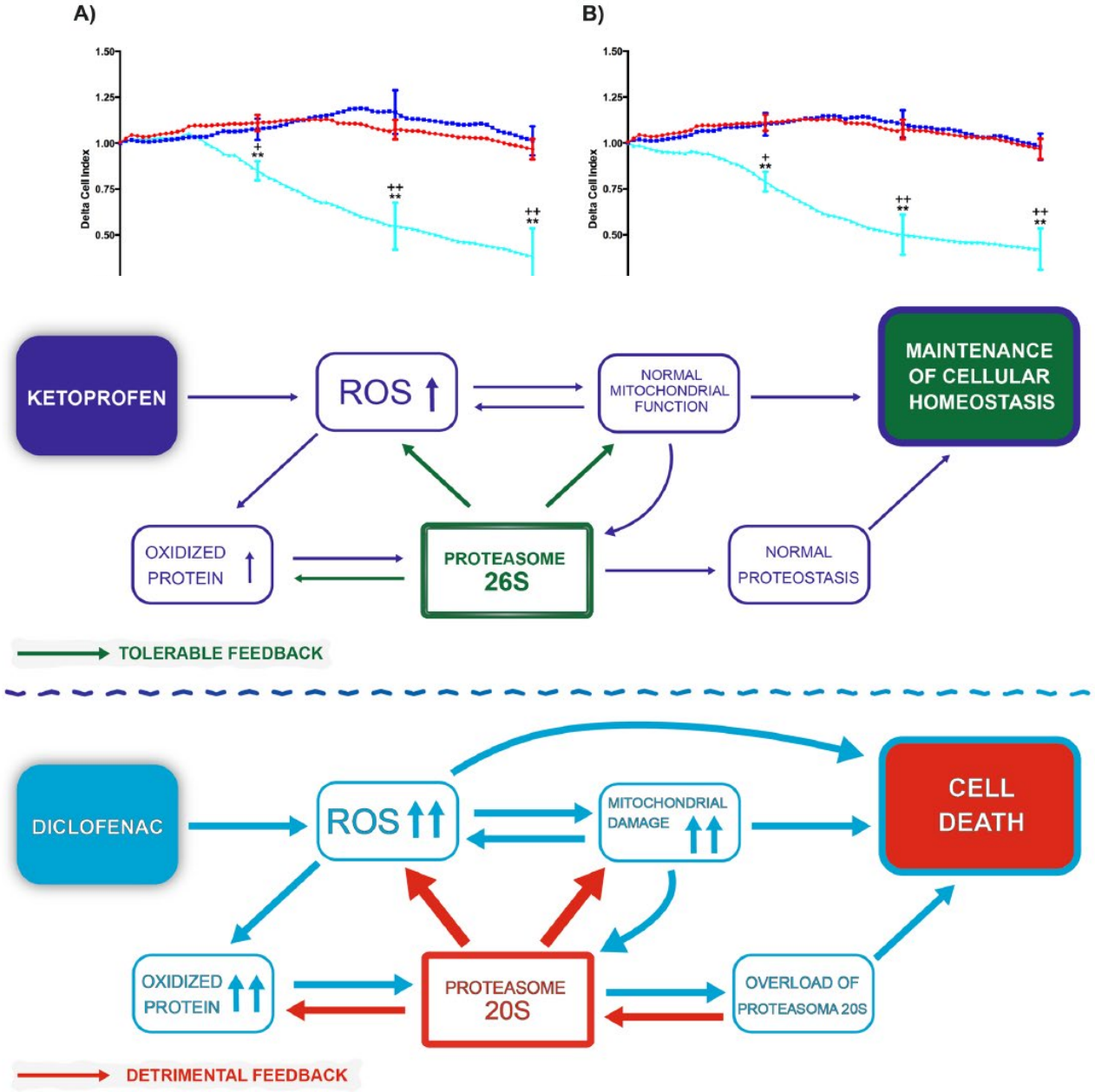


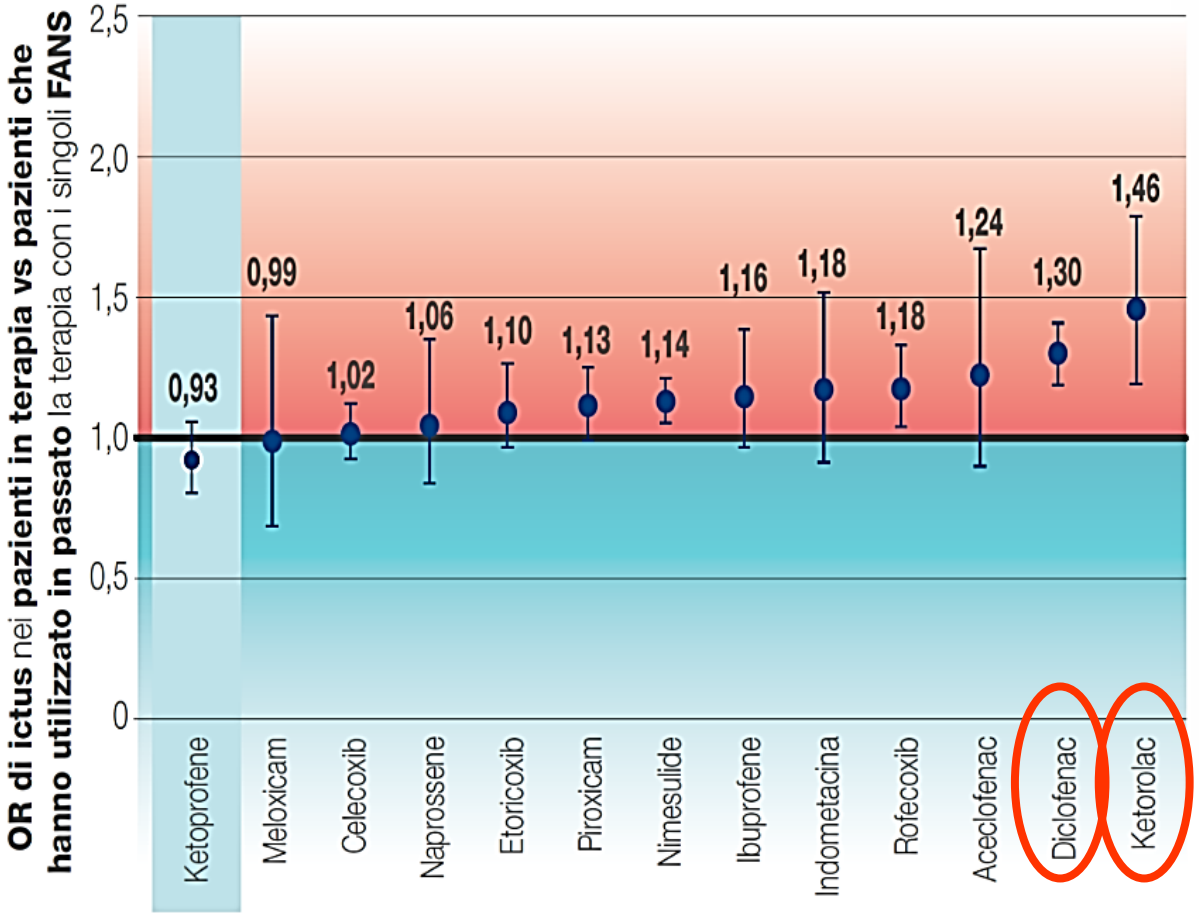
Figure 9. Schematic representation of the proposed mechanism of K versus Dic.

FANS E RISCHIO DI ICTUS – Pubblicazioni SOS

Progetto SOS

- **Commissionato** dall'EMA e finanziato dalla Commissione Europea

Dati raccolti da 7 database di Italia, Germania, Francia e UK che attingono a un bacino di 35 milioni di soggetti



SOS Final report 2012

FANS E RISCHIO DI INFARTO DEL MIOCARDIO – Pubblicazioni SOS

RESEARCH ARTICLE

Risk of acute myocardial infarction during use of individual NSAIDs: A nested case-control study from the SOS project

Gwen M. C. Masclee[1], Huub Straatman[2], Andrea Arfè[3], Jordi Castellsague[4], Edeltraut Garbe[5], Ron Herings[2], Bianca Kollhorst[5], Silvia Lucchi[6], Susana Perez-Gutthann[4], Silvana Romio[3,7], René Schade[7], Tania Schink[5], Martijn J. Schuemie[7], Lorenza Scotti[3], Cristina Varas-Lorenzo[4], Vera E. Valkhoff[8], Marco Villa[6], Miriam C. J. M. Sturkenboom[9]*

Ketorolac è risultato il FANS con rischio di insorgenza di IMA più elevato

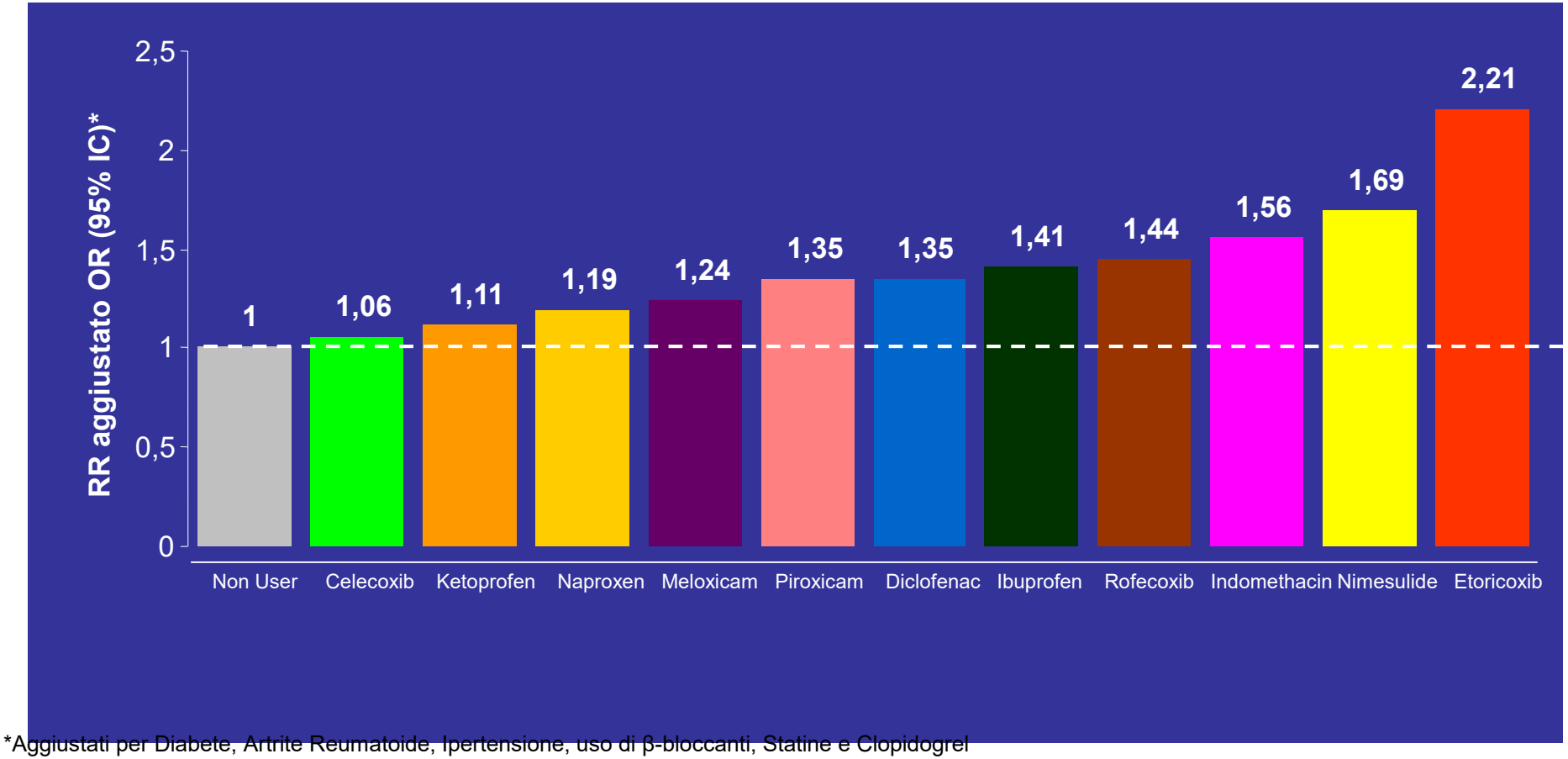
Altri FANS come indometacina, **diclofenac,** piroxicam, **ibuprofene, naprossene**, meloxicam, nimesulide, etoricoxib, rofecoxib e celecoxib sono associati ad un aumento del rischio di IMA

ketoprofene presenta **un Odds Ratio tra i più bassi** rispetto agli altri FANS valutati

Masclee et al. 2018

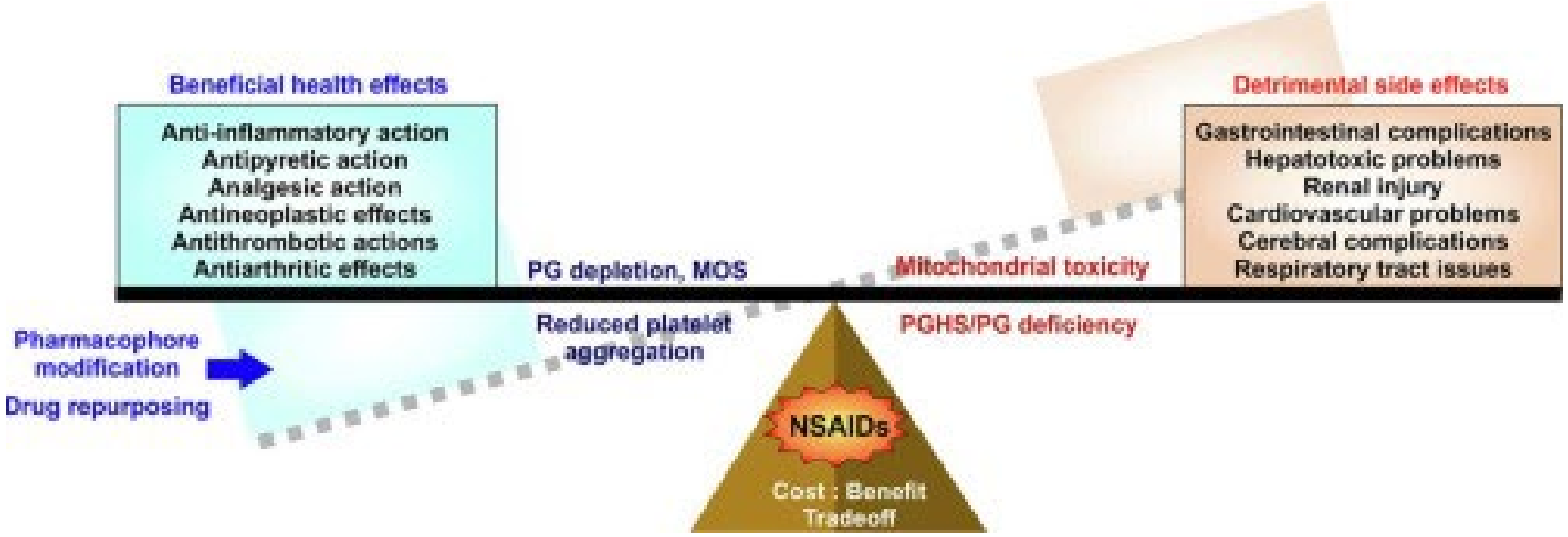
Studio di popolazione caso-controllo (Finlandia)

Rischio di prima ospedalizzazione per IMA in pazienti in corso di terapia con Coxib e FANS tradizionali nella popolazione gnerale



*Aggiustati per Diabete, Artrite Reumatoide, Ipertensione, uso di β-bloccanti, Statine e Clopidogrel
Finnish Hospital Discharge Register n. 172.258 pazienti

European Heart Journal May 2006-27,1657-1663


Beneficial health effects
Anti-inflammatory action
Antipyretic action
Analgesic action
Antineoplastic effects
Antithrombotic actions
Antiarthritic effects
Detrimental side effects
Gastrointestinal complications
Hepatotoxic problems
Renal injury
Cardiovascular problems
Cerebral complications
Respiratory tract issues
PG depletion, MOS
Mitochondrial toxicity
Reduced platelet aggregation
PGHS/PG deficiency
Pharmacophore modification
Drug repurposing
NSAIDs
Cost : Benefit Tradeoff

Grazie