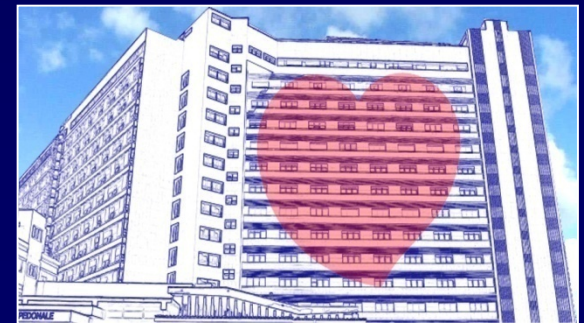


# **NON STEROIDAL ANTI-INFLAMMATORY DRUGS AND CARDIOVASCULAR RISK**

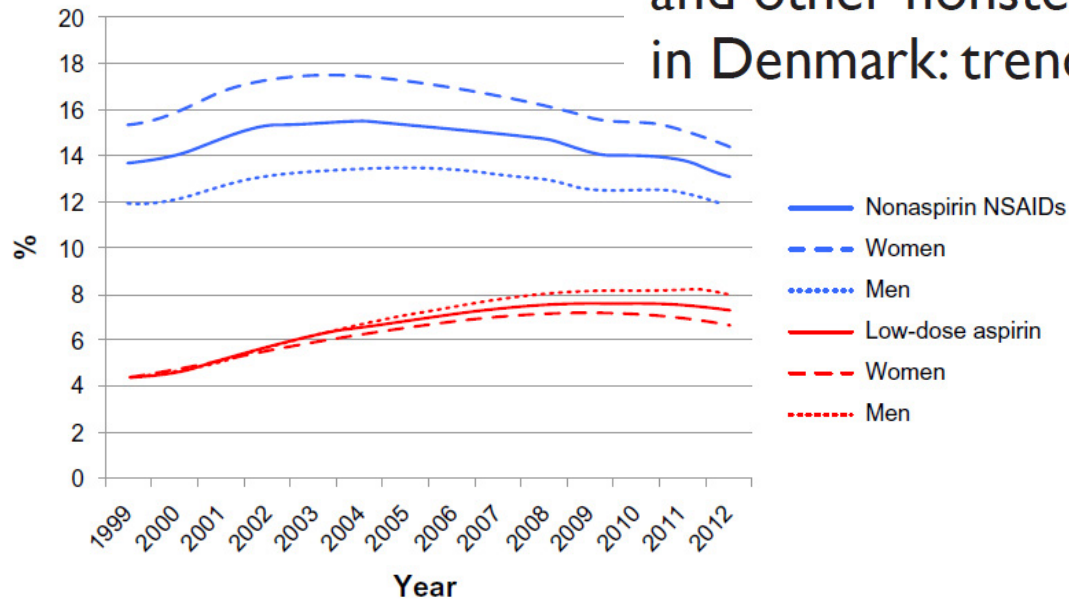
**Advances in Cardiac Arrhythmias  
and Great Innovations in Cardiology**

**Torino, October 15, 2016**

**Giuseppe Di Pasquale  
Direttore Dipartimento Medico ASL Bologna  
Direttore Unità Operativa Cardiologia  
Ospedale Maggiore, Bologna**



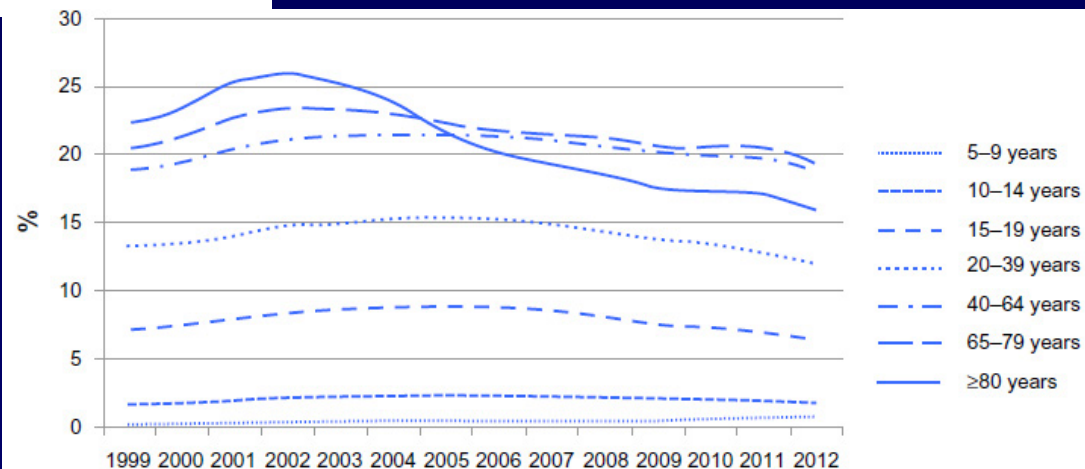
# Potential of prescription registries to capture individual-level use of aspirin and other nonsteroidal anti-inflammatory drugs in Denmark: trends in utilization 1999–2012



The 1-year prevalence of the Danish population redeeming a prescription

## Nonaspirin NSAIDs

Each year, around 13%–15% of the total Danish population redeemed at least one prescription of nonaspirin NSAID between 1999 and 2012 (Table 1). From age 10–15 years, the prevalence of use increased markedly with age (Figure 2B).



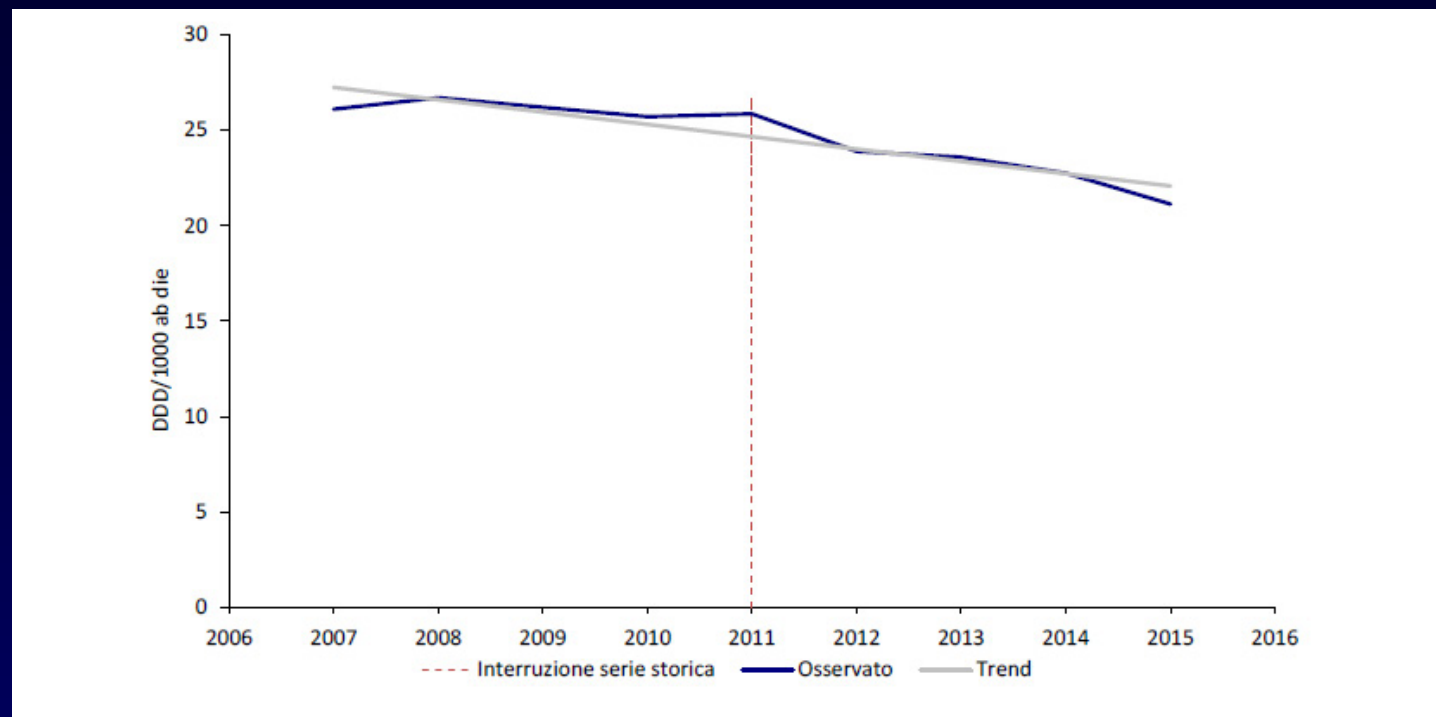
**Tabella 7.4.3.** Primi trenta principi attivi di Automedicazione (SOP e OTC) a maggiore spesa nel 2015

ATC	Principio attivo	DDD/1000 ab die	Spesa (milioni)	%*	Δ % 15-14	% SOP	% OTC
M	Diclofenac	8,9	149,5	6,2	6,1	4,4	95,6
M	Ibuprofene	2,3	128,4	5,3	1,1	21,7	78,3
N	Paracetamolo	2,7	116,8	4,8	7,3	95,6	4,4
A	Microorganismi antidiarroici	2,0	93,5	3,9	9,1	-	100,0
A	Vari	3,9	79,8	3,3	4,4	0,8	99,2
C	Diosmina	3,0	62,3	2,6	3,3	100,0	-
N	Paracetamolo, associazioni escl. psicolettici	1,9	61,1	2,5	7,0	2,8	97,2
R	Ambroxolo	0,9	58,0	2,4	4,7	72,9	27,1
N	Acido acetilsalicilico, ass. escl. psicolettici						
R	Carbocisteina						
R	Pseudoefedrina, associazioni						
D	Altri cicatrizzanti						
A	Glicerolo (clisteri)						
A	Loperamide						
R	Nafazolina						
M	Ketoprofene						
A	Polivitaminici e altri minerali, incl. associazio						
R	Antisettici vari						
A	Glicerolo (altri farmaci per la costipazione)						
B	Elettroliti						
R	Ossimetazolina	2,4	21,9	0,9	1,9	-	100,0
A	Lattuloso	2,3	19,9	0,8	-2,8	63,6	36,4
S	Nafazolina	5,8	19,2	0,8	0,9	-	100,0
D	Tioconazolo	0,4	19,1	0,8	9,9	-	100,0
R	Bromexina	0,8	18,8	0,8	3,4	-	100,0
M	Diclofenac	0,5	18,8	0,8	65,2	-	100,0
D	Altri dermatologici	0,4	18,8	0,8	-4,4	15,2	84,8
A	Saccharomyces boulardi 17	0,2	18,6	0,8	16,8	25,2	74,8
A	Magnesio pidolato	0,5	18,6	0,8	1,5	0,0	100,0
R	Derivati dell'oppio ed espettoranti	0,5	18,4	0,8	33,4	-	100,0
	Altri	74,6	1.104,6	45,6	2,3		
	<b>Totale</b>	<b>135,2</b>	<b>2.423,7</b>	<b>100,0</b>	<b>4,6</b>		

Gruppo	Sottogruppo	Spesa totale (milioni)	% su spesa SSN	DDD totali (milioni)
<b>Farmaci antinfiammatori non steroidici</b>		<b>209,2</b>	<b>1,0</b>	<b>468,9</b>
	Altri FANS per via sistemica	123,2	0,6	357,8
	Anti-cox 2	78,9	0,4	98,4
	Ketorolac	7,1	0,0	12,7

\*La percentuale è calcolata sul totale della spesa lorda

# FANS: Andamento temporale del consumo 2007-2015



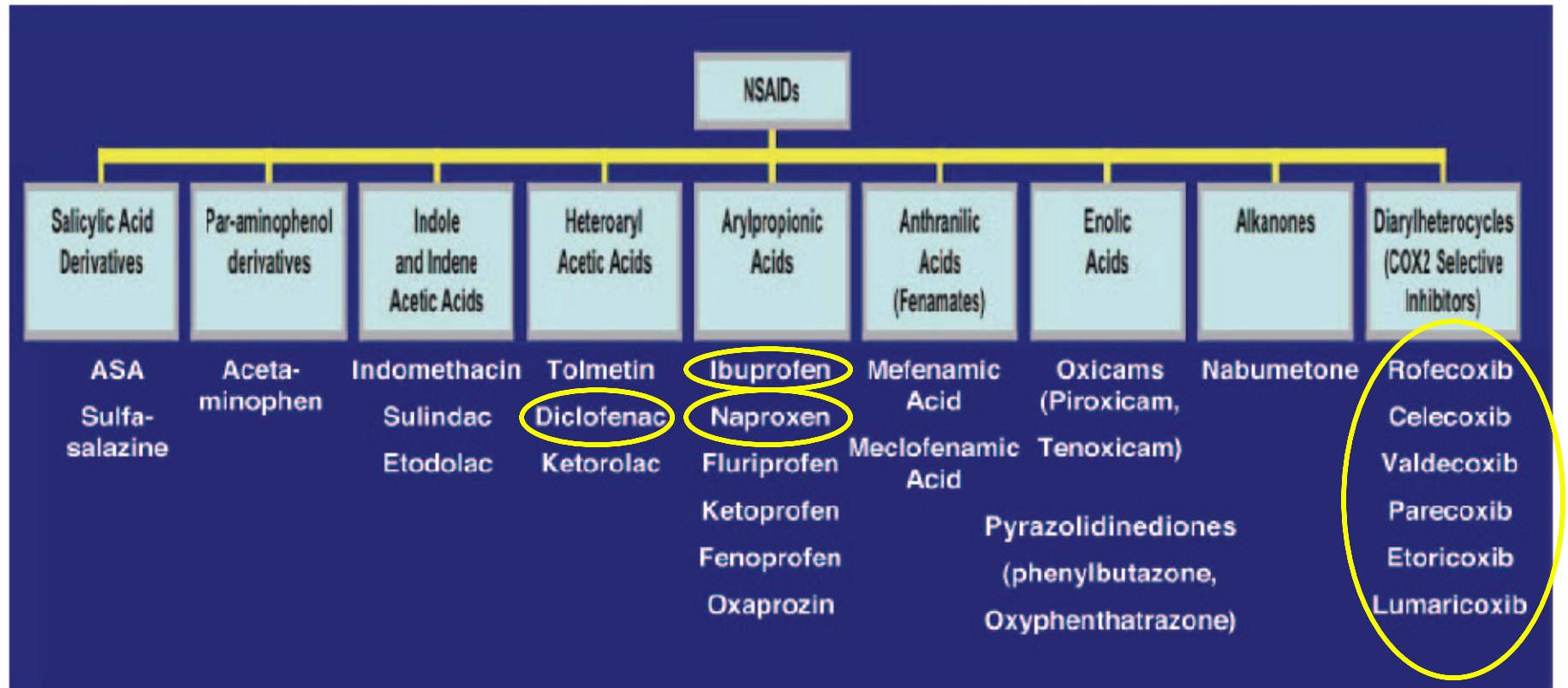
**Tabella 7.2.9a.** Farmaci antiinfiammatori non steroidei (FANS), (DDD/1000 ab die) per categoria terapeutica e per sostanza: confronto 2007-2015

Sottogruppi e sostanze	2007	2008	2009	2010	2011*	2012	2013	2014	2015	Δ %
FANS	26,1	26,7	26,2	25,7	25,8	23,9	23,6	22,8	21,1	-7,1

Osservatorio Nazionale sull'impiego dei Medicinali.  
L'uso dei farmaci in Italia. Rapporto Nazionale 2015.  
Roma: Agenzia Italiana del Farmaco, 2016.



# The 9 Chemical Groupings of NSAIDs



Antman EL et al, Circulation 2007;115:1634-1642

# The Role of the COX Isozymes

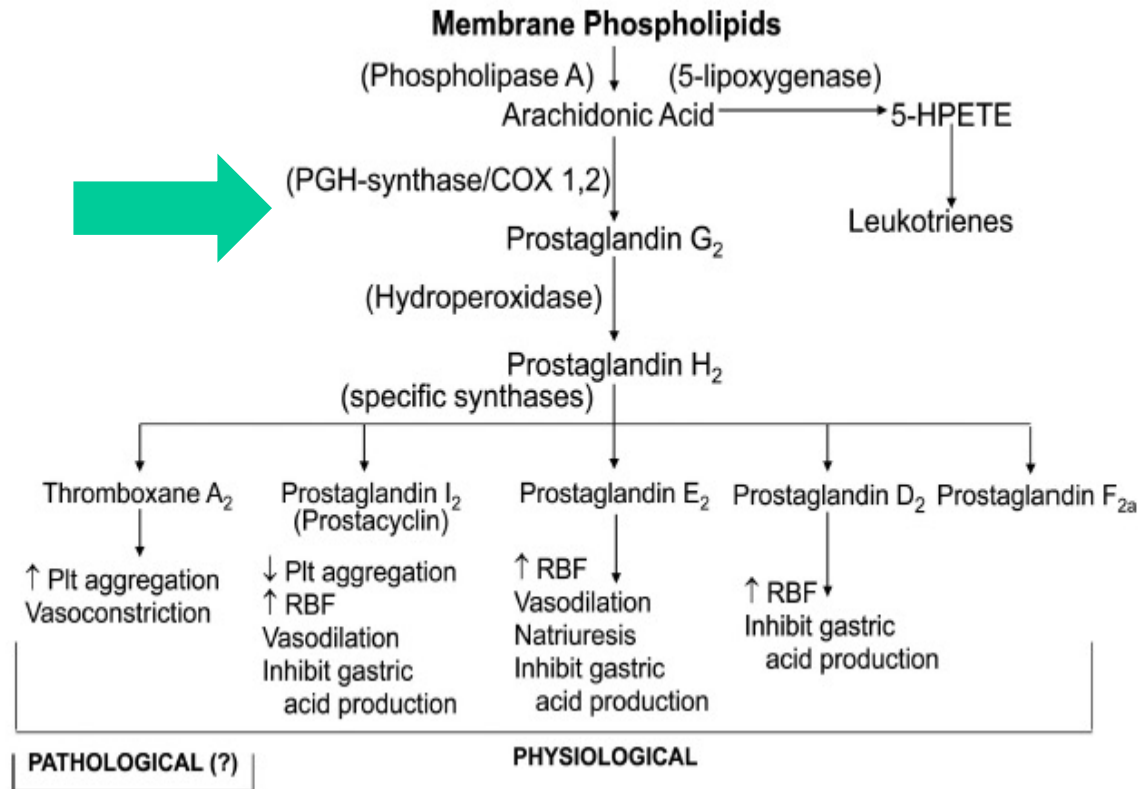
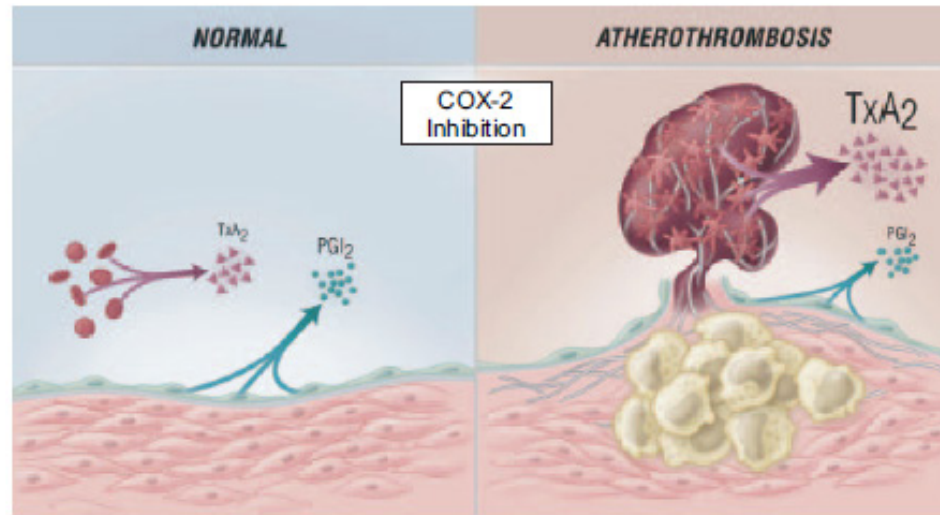
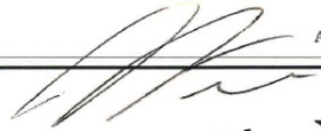


Figure 5. The production of prostaglandins from arachidonic acid and their physiological effects.

# Consequences of COX inhibition in normal and atherosclerotic arteries



**Figure 5.** Consequences of COX inhibition for prostacyclin and TXA<sub>2</sub> production in normal and atherosclerotic arteries. Endothelial cells are shown as a source of prostacyclin (PGI<sub>2</sub>) and platelets as a source of TXA<sub>2</sub>. COX-2 inhibition suppresses COX-2-dependent PGI<sub>2</sub> production in endothelial cells, which has only a marginal effect on the net antithrombotic balance owing to the importance of COX-1 as a source of PGI<sub>2</sub> in the normal state. In the setting of atherosclerosis, however, COX-2 plays a greater role as a source of PGI<sub>2</sub>, and more TXA<sub>2</sub> is produced; thus, inhibiting COX-2 has a more profound effect on prostanoid balance, favoring TXA<sub>2</sub> production and promoting platelet-dependent thrombosis. Modified and reproduced from Antman et al<sup>11</sup> with permission from the American Heart Association. Copyright 2005.



# The NEW ENGLAND JOURNAL of MEDICINE

VOL. 352 NO. 11

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MARCH 17, 2005

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## 1061 THIS WEEK IN THE JOURNAL

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- 1067 2015 — The Future of Medical Libraries  
D.A.B. Lindberg and B.L. Humphreys
- 1068 Quiet in the Library T.H. Lee

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in a Clinical Trial for Colorectal Adenoma Prevention  
S.D. Solomon and Others
- X 1081 Complications of the COX-2 Inhibitors Parecoxib  
and Valdecoxib after Cardiac Surgery  
N.A. Nussmeier and Others
- X 1092 Cardiovascular Events Associated with Rofecoxib  
in a Colorectal Adenoma Chemoprevention Trial  
R.S. Bresalier and Others

### CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

- 1122 A Boy with Pain in the Right Thigh  
M.C. Gebhardt, D.I. Rosenthal, and P.M. Arnell

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J.M. Drazen
- 1133 COX-2 Inhibitors — Lessons in Drug Safety  
B.M. Psaty and C.D. Furberg
- 1135 Deadweight? — The Influence of Obesity  
on Longevity  
S.H. Preston

### SPECIAL REPORT

- 1138 A Potential Decline in Life Expectancy  
in the United States in the 21st Century

# N Engl J Med March 17, 2005

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

APPROVe Trial. Bresalier *et al.* N Engl J Med 2005;352:1092-102

The NEW ENGLAND  
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ESTABLISHED IN 1812

MARCH 17, 2005

VOL. 352 NO. 11

## Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention

The APC Study . Solomon SD *et al.* N Engl J Med 2005;352:1071-1080

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib after Cardiac Surgery

Nussmeier *et al.*, N Engl J Med 2005;352:1081-1091



## **AHA Science Advisory**

### **The Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) A Science Advisory From the American Heart Association**

Joel S. Bennett, MD; Alan Daugherty, PhD; David Herrington, MD, MHS; Philip Greenland, MD;  
Harold Roberts, MD; Kathryn A. Taubert, PhD

**Circulation 2005;111: 1713-1716**

**This high overall use is a concern as these drugs are associated with risk of myocardial infarction and death also in the otherwise healthy general population.**

### Diclofenac sodium enteric-coated tablets

Tablets of 25 mg, 50 mg, and 75 mg

Rx only

Prescribing information

#### Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS.)
- Voltaren® (diclofenac sodium enteric-coated tablets) is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

#### Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).

**Figure 3.** Black box warning for COX-2–selective drugs. This black box warning statement now appears in the package insert (July 2005) for celecoxib, the only coxib currently on the market in the United States, emphasizing the increased risk of cardiovascular events with its use.

**Figure 2.** Black box warning for NSAIDs. This black box warning statement now appears in the package insert for agents in the “traditional” NSAID group, emphasizing the increased risk of cardiovascular events with their use. This example is from the package insert (January 2006) of diclofenac, a commonly prescribed NSAID. Similar black box warnings appear in the package inserts for other NSAIDs (see Figure 4).

### Celecoxib capsules

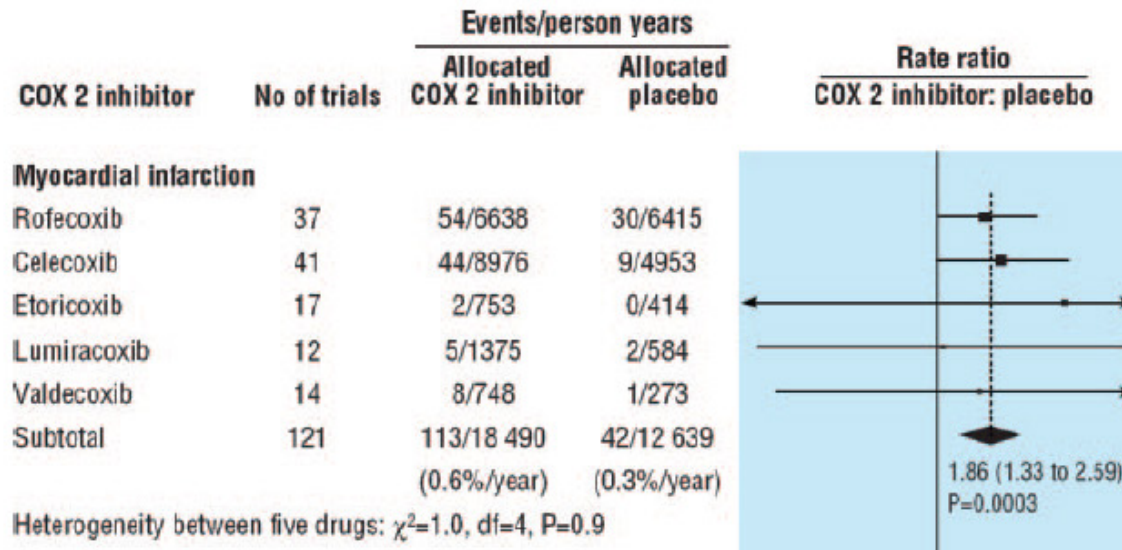
#### Cardiovascular Risk

- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS and CLINICAL TRIALS).
- CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

#### Gastrointestinal Risk

- NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).

# Comparison of effects of different selective COX-2 inhibitors vs placebo on myocardial infarction



**Figure 1.** Comparison of effects of different selective COX-2 inhibitors vs placebo on myocardial infarction. Event numbers and person-years of exposure, with corresponding mean annual event rates in parentheses, are presented for patients allocated to selective COX-2 inhibitor or placebo. Event rate ratios for pooled data with 95% CIs are indicated by a diamond; rate ratios for individual selective COX-2 inhibitors, with 99% CIs, are indicated by a square and horizontal line. Diamonds to the right of the solid line indicate hazard with a selective COX-2 inhibitor compared with placebo. As noted, there was a significant increase in the rate ratio for myocardial infarction with COX-2 inhibitors compared with placebo. Similar analyses (data not shown) include rate ratios of 1.42 (1.13 to 1.78;  $P=0.003$ ) for vascular events, 1.02 (0.71 to 1.47;  $P=0.9$ ) for stroke, and 1.49 (0.97 to 2.29;  $P=0.07$ ) for vascular death with COX-2 inhibitors compared with placebo. Modified and reproduced from Kearney et al,<sup>2</sup> with permission from the BMJ Publishing Group.

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# Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials



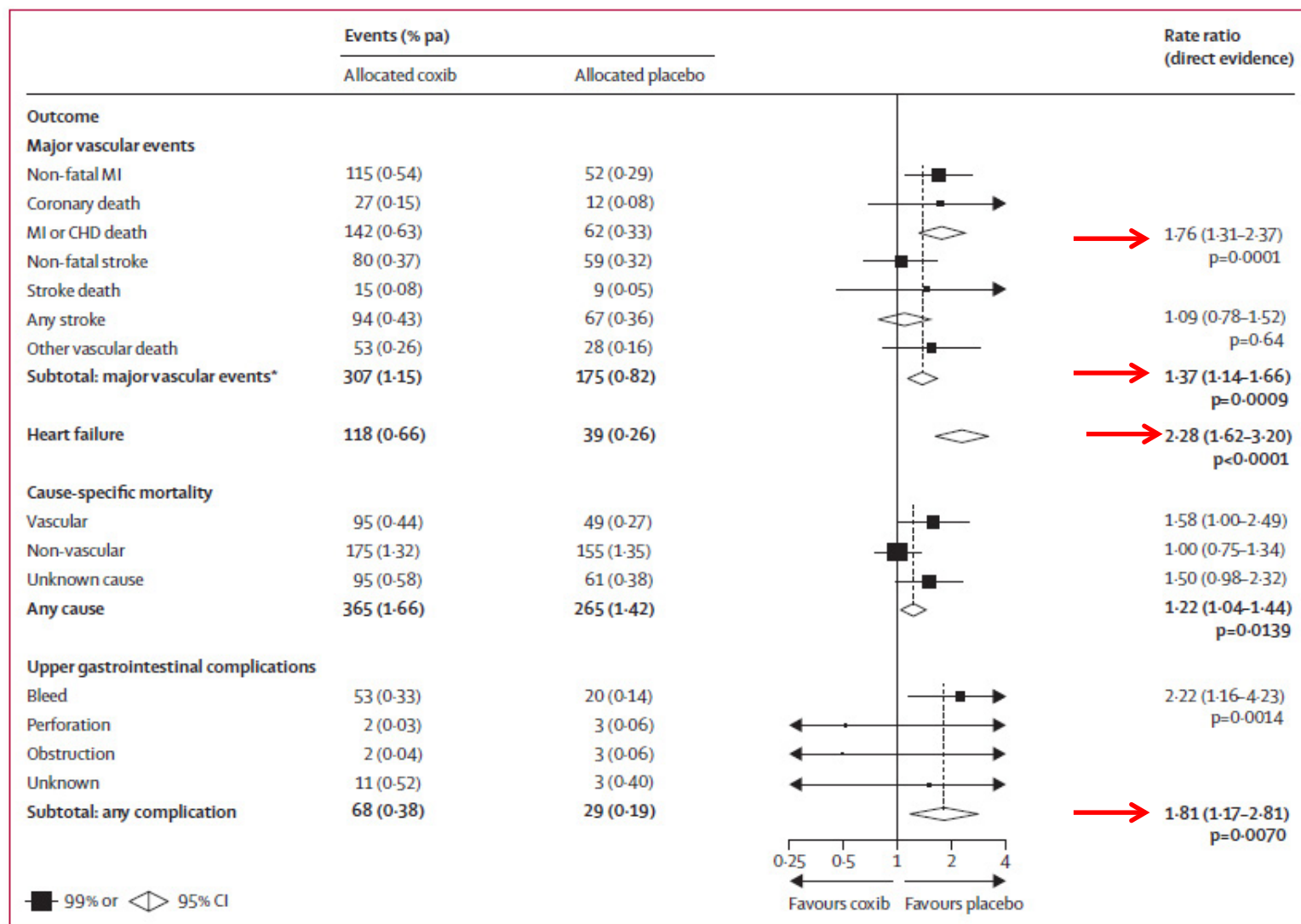
*Coxib and traditional NSAID Trialists' (CNT) Collaboration\**

**Data from 280 RCTs of NSAIDs vs placebo (No. pts = 124.513) and 474 RCTs of one NSAID vs another NSAID (No. pts = 229.296)**

**Lancet 2013;382: 769-779**

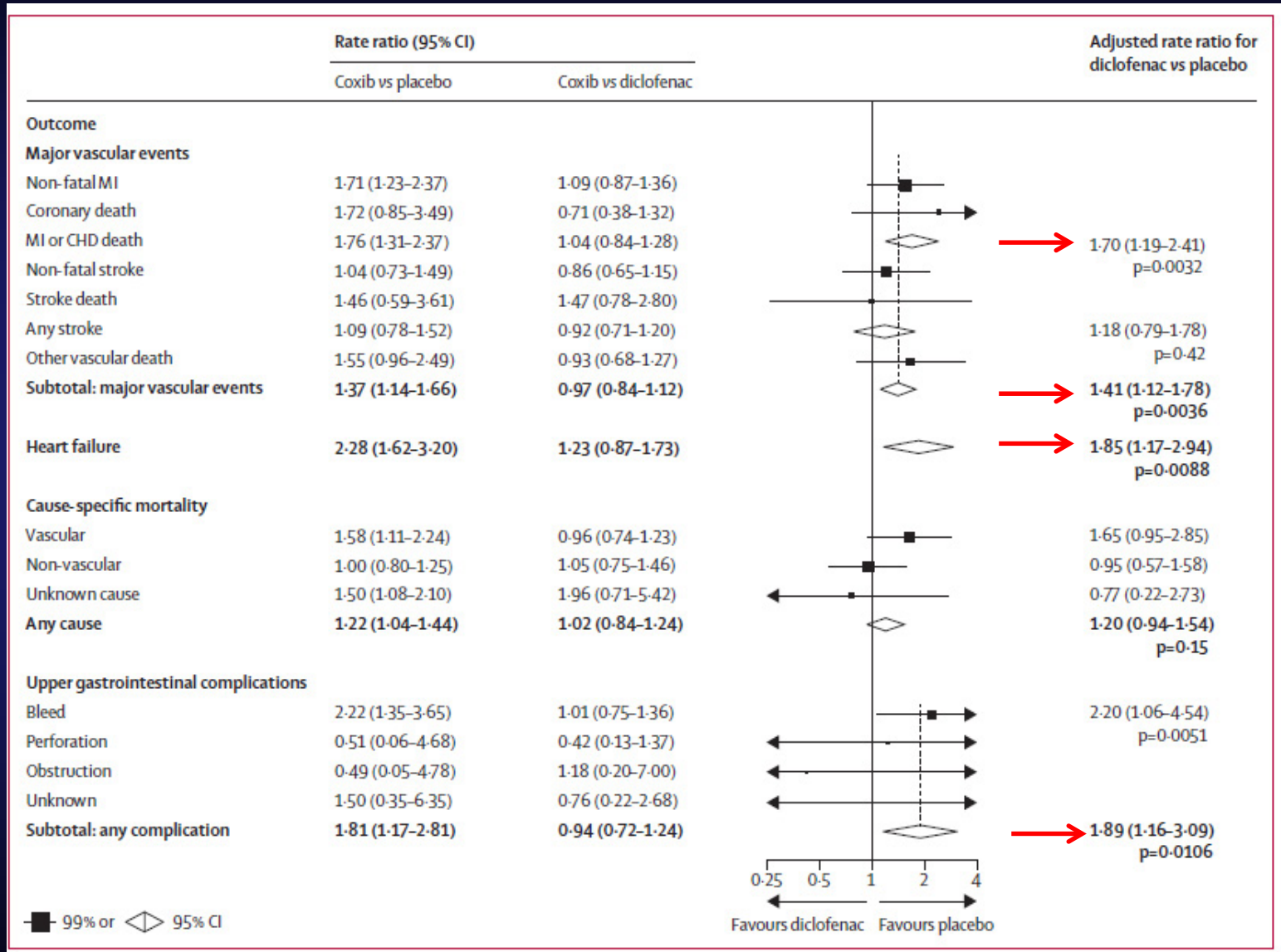


# Effects of coxib therapy on major vascular events, heart failure, cause-specific mortality, and upper gastrointestinal complications

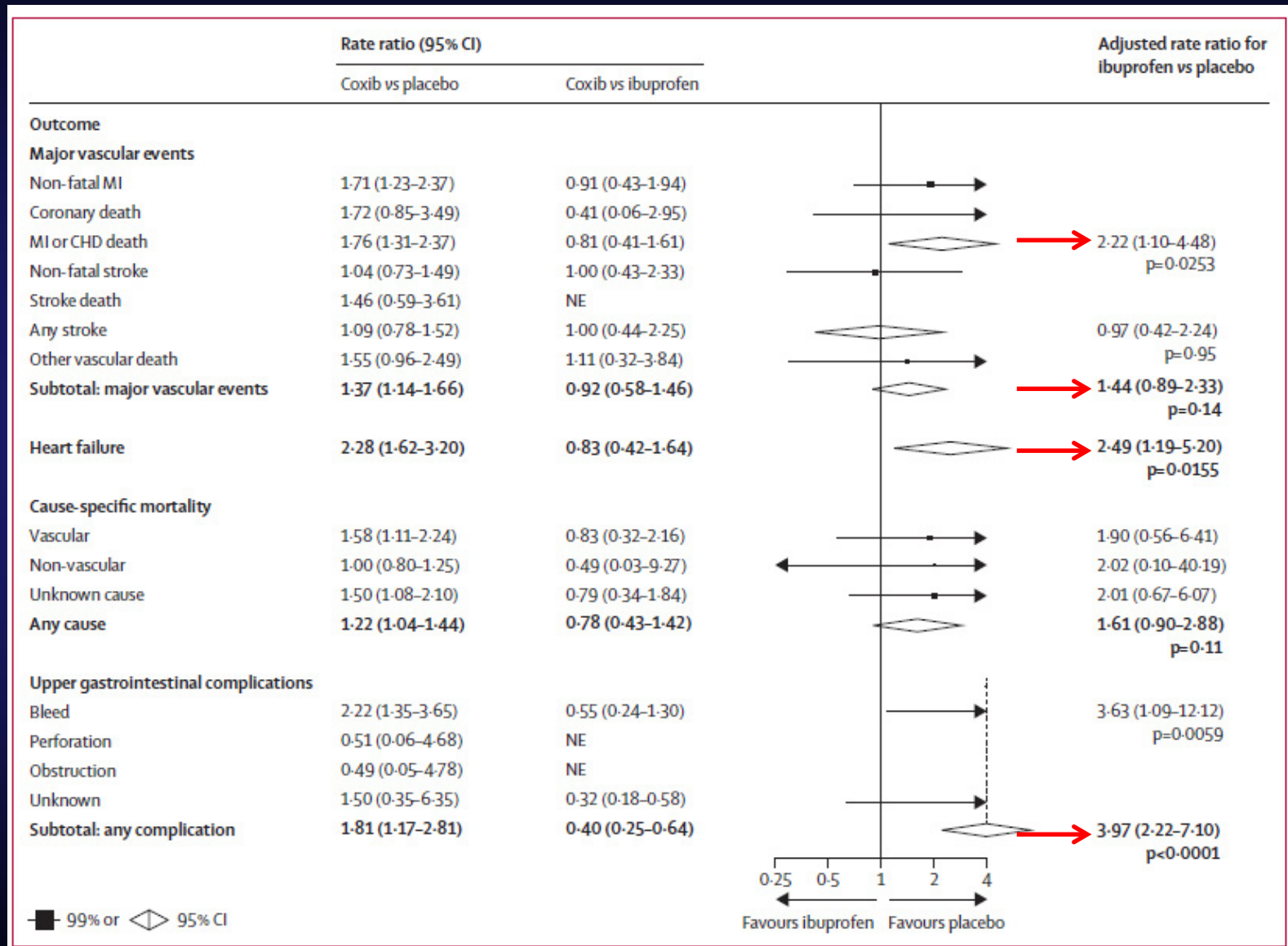




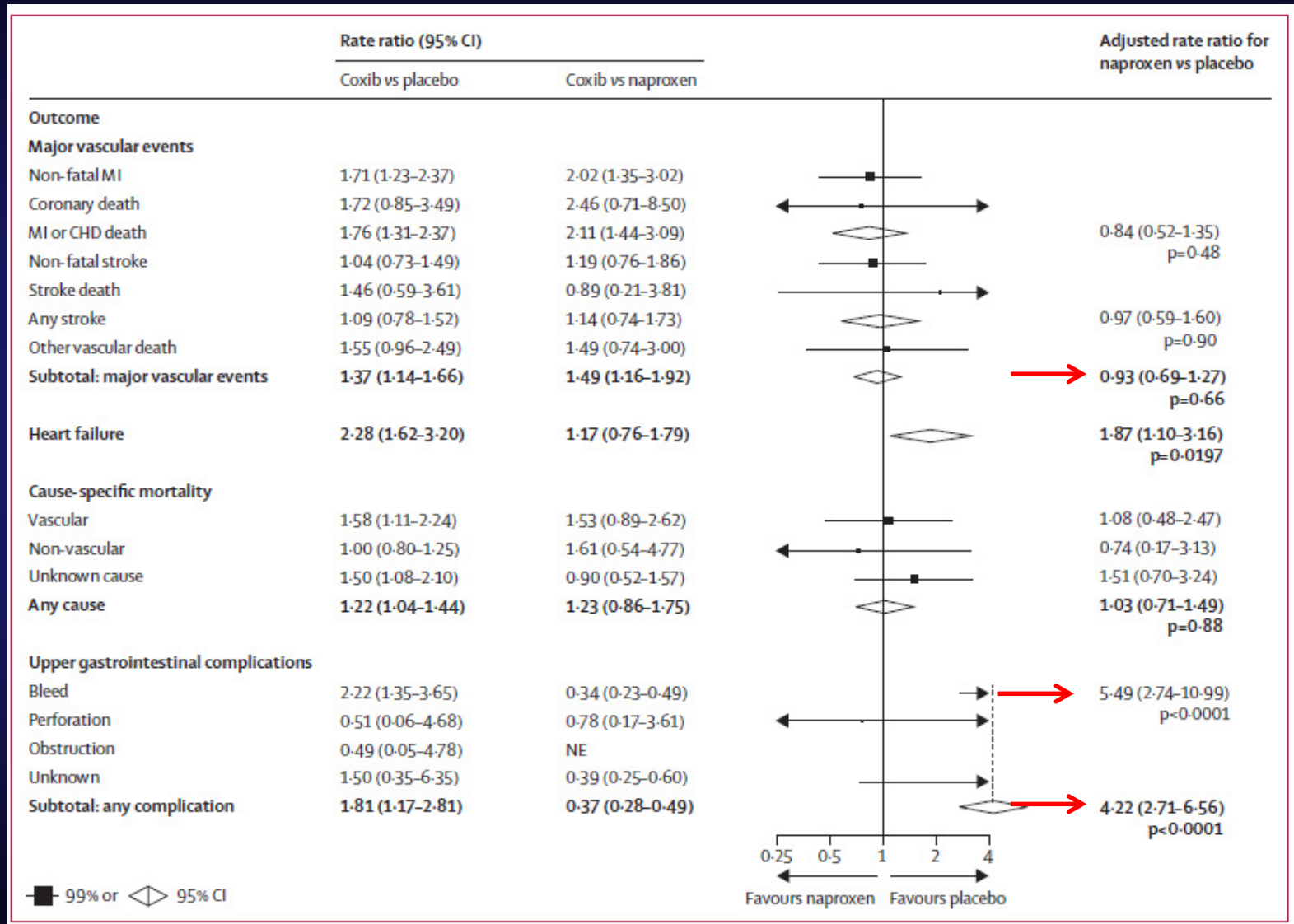
# Effects of DICLOFENAC on major vascular events, heart failure, cause-specific mortality, and upper gastrointestinal complications



# Effects of IBUPROFEN on major vascular events, heart failure, cause-specific mortality, and upper gastrointestinal complications



# Effects of NAPROXEN on major vascular events, heart failure, cause-specific mortality, and upper gastrointestinal complications



# Evidence in patients with myocardial infarction

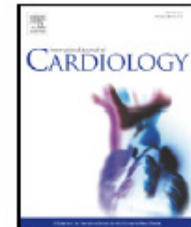
International Journal of Cardiology 168 (2013) 832–837



Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: [www.elsevier.com/locate/ijcard](http://www.elsevier.com/locate/ijcard)



Ongoing treatment with non-steroidal anti-inflammatory drugs at time of admission is associated with poorer prognosis in patients with first-time acute myocardial infarction<sup>☆</sup>

Morten Lamberts<sup>a,\*</sup>, Emil L. Fosbøl<sup>b</sup>, Anne-Marie S. Olsen<sup>a</sup>, Morten L. Hansen<sup>a</sup>, Frederik Folke<sup>a</sup>, Søren L. Kristensen<sup>a</sup>, Jonas B. Olesen<sup>a</sup>, Peter R. Hansen<sup>a</sup>, Lars Køber<sup>d</sup>, Christian Torp-Pedersen<sup>a</sup>, Gunnar H. Gislason<sup>a,c</sup>

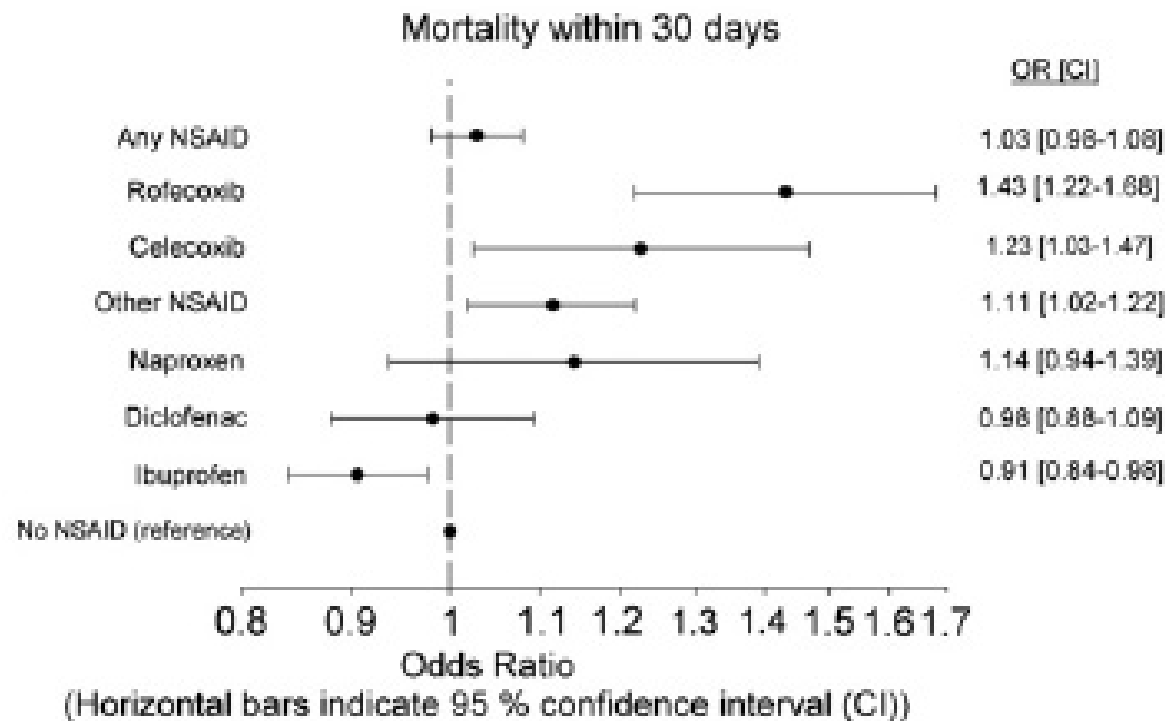
<sup>a</sup> Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark

<sup>b</sup> Duke Clinical Research Institute, Durham, North Carolina, USA

<sup>c</sup> National Institute of Public Health, Copenhagen, Denmark

<sup>d</sup> Department of Cardiology, The Heart Center, Rigshospitalet, Copenhagen, Denmark

Int J Cardiol 2013; 168 : 832-837



**Fig. 4.** Mortality within 30 days – odds ratios for the risk of death associated with use of selective COX-2 inhibitors and non-selective NSAIDs after admission for first-time MI. Adjusted for age, gender, year of MI, concomitant medical therapy, and comorbidity. Reference group: no use of COX-2 inhibitors or NSAIDs. Bars indicate 95% confidence intervals.



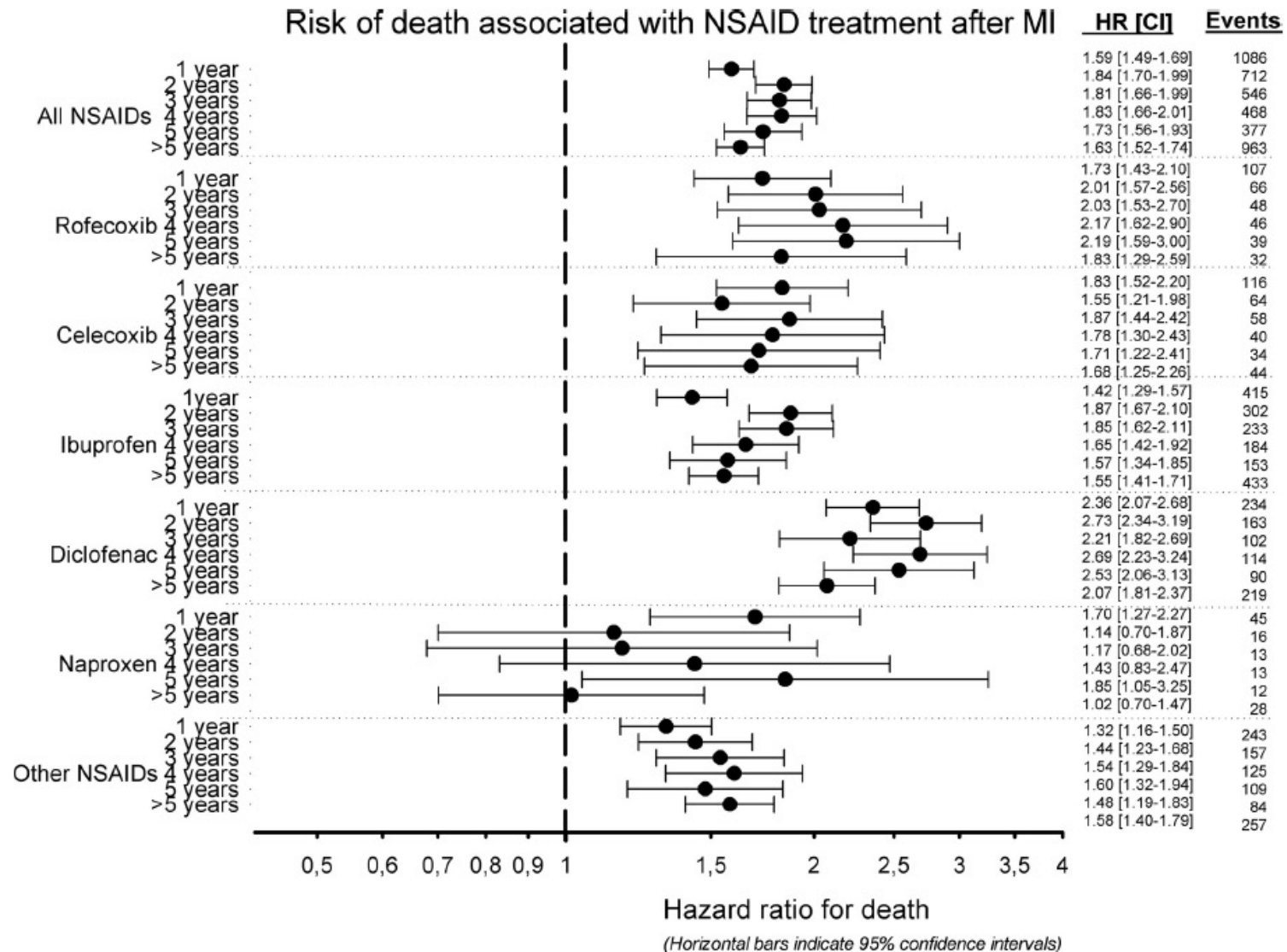
## **Epidemiology and Prevention**

# **Long-Term Cardiovascular Risk of Nonsteroidal Anti-Inflammatory Drug Use According to Time Passed After First-Time Myocardial Infarction A Nationwide Cohort Study**

Anne-Marie Schjerning Olsen, MD; Emil L. Fosbøl, MD, PhD; Jesper Lindhardsen, MD;

**Circulation 2012; 126: 1955 - 1963**

- **Cohort study**
- **Denmark (nationwide)**
- **1997-2009**
- **First-time MI (n=99,187)**
- **NSAIDs (all types)**
- **re-MI or coronary death, or all-cause death**



**Figure 3.** Time-dependent Cox proportional hazards analysis of the risk of death according to the time of NSAID treatment among patients with previous myocardial infarction (MI). NSAID indicates nonsteroidal anti-inflammatory drug; HR, hazard ratio; and CI, confidence interval.

Original Investigation

# Association of NSAID Use With Risk of Bleeding and Cardiovascular Events in Patients Receiving Antithrombotic Therapy After Myocardial Infarction

Cohort study, Denmark (nationwide), 2002-2011

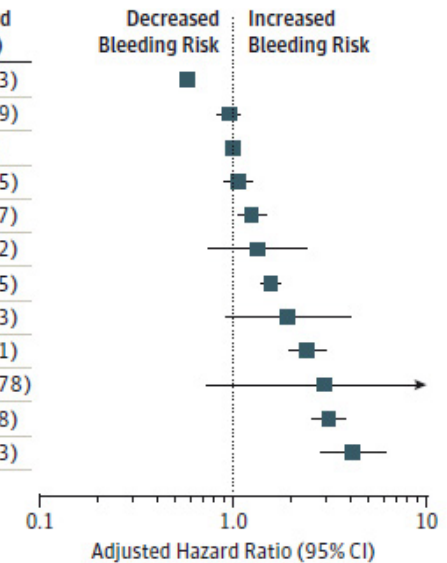
- MI survivors >30 y (n=61,971)
- NSAID + combination of aspirin, clopidogrel, vitamin K-antagonists
- Outcomes: serious bleeding, MACE (CV death, re-MI, stroke)

Scherning Olsen AM et al, JAMA 2015

# Bleeding and CV Risk With and Without Use of Any NSAID in Pts With Prior MI

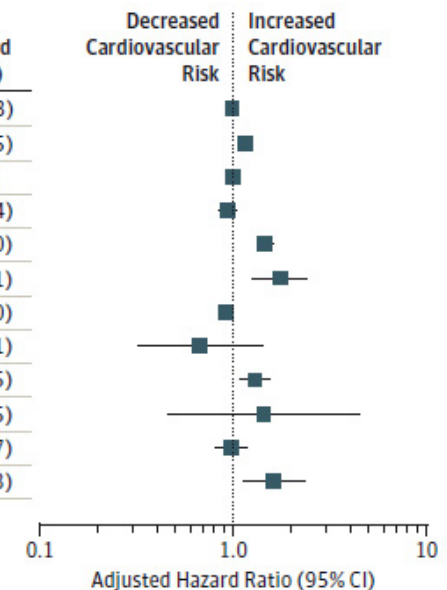
## A Bleeding risk

	Events, No.	Sample Size, No.	Crude Rate (95% CI), Events per 100 Person-Years	Adjusted Hazard Ratio (95% CI)
Aspirin	2109	221 458	1.5 (1.5-1.6)	0.58 (0.53-0.63)
Clopidogrel	258	35 814	3.3 (2.9-3.7)	0.95 (0.83-1.09)
Clopidogrel + aspirin	1184	99 468	3.3 (3.1-3.5)	1 [Reference]
Oral anticoagulants	175	24 588	4.0 (3.5-4.7)	1.06 (0.90-1.25)
Aspirin + NSAID	176	57 016	3.2 (2.8-3.8)	1.24 (1.05-1.47)
Clopidogrel + NSAID	11	3 419	4.1 (2.3-7.3)	1.34 (0.74-2.42)
Oral anticoagulants + single antiplatelet	477	49 504	5.2 (4.7-5.7)	1.56 (1.39-1.75)
Oral anticoagulants + NSAID	7	1 478	7.2 (3.4-15.1)	1.92 (0.91-4.03)
Clopidogrel + aspirin + NSAID	83	14 105	7.6 (6.2-9.5)	2.41 (1.93-3.01)
Triple therapy + NSAID	2	382	10.0 (2.5-39.9)	2.94 (0.73-11.78)
Triple therapy	116	8 250	12.7 (10.6-15.2)	3.12 (2.57-3.78)
Oral anticoagulants + single antiplatelet + NSAID	26	2 922	13.1 (8.9-19.3)	4.15 (2.81-6.13)



## B Cardiovascular risk

	Events, No.	Sample Size, No.	Crude Rate (95% CI), Events per 100 Person-Years	Adjusted Hazard Ratio (95% CI)
Aspirin	9194	209 681	7.1 (6.9-7.2)	0.98 (0.94-1.03)
Clopidogrel	822	32 494	11.6 (10.8-12.4)	1.16 (1.07-1.25)
Clopidogrel + aspirin	3229	90 153	10.0 (9.7-10.4)	1 [Reference]
Oral anticoagulants	454	22 979	11.2 (10.2-12.2)	0.94 (0.85-1.04)
Aspirin + NSAID	529	54 076	10.3 (9.4-11.2)	1.46 (1.32-1.60)
Clopidogrel + NSAID	37	3 073	15.4 (11.2-21.3)	1.75 (1.26-2.41)
Oral anticoagulants + single antiplatelet	822	45 292	9.7 (9.0-10.3)	0.91 (0.84-1.00)
Oral anticoagulants + NSAID	7	1 362	7.7 (3.7-16.2)	0.67 (0.32-1.41)
Clopidogrel + aspirin + NSAID	123	12 608	12.7 (10.6-15.1)	1.30 (1.08-1.55)
Triple therapy + NSAID	3	324	18.8 (6.0-58.2)	1.44 (0.46-4.45)
Triple therapy	119	7 213	14.9 (12.5-17.9)	0.98 (0.82-1.17)
Oral anticoagulants + single antiplatelet + NSAID	30	2 722	16.0 (11.2-22.8)	1.62 (1.13-2.33)





 OPEN ACCESS

## Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study

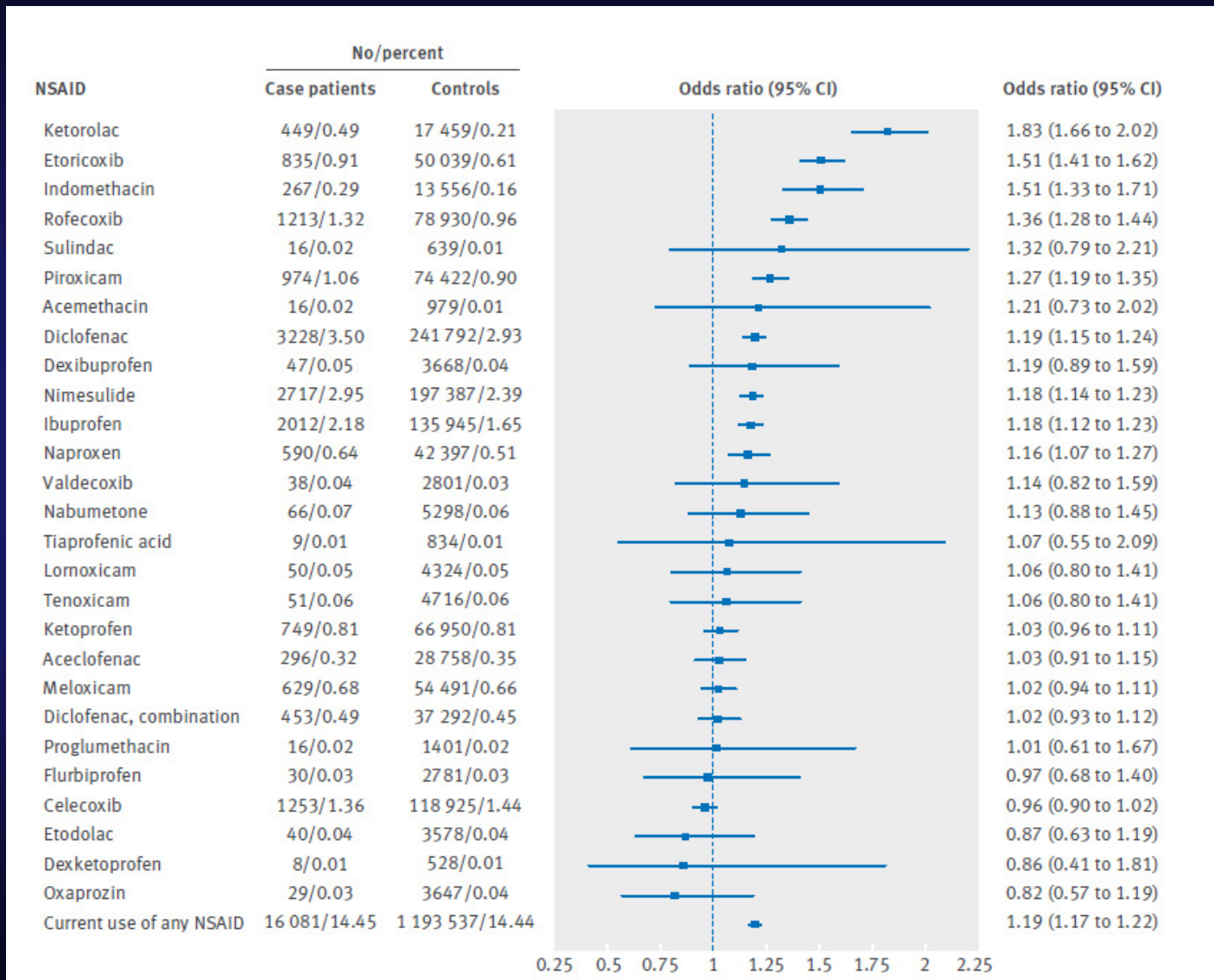
Andrea Arfè,<sup>1</sup> Lorenza Scotti,<sup>1</sup> Cristina Varas-Lorenzo,<sup>2</sup> Federica Nicotra,<sup>1</sup> Antonella Zambon,<sup>1</sup> Bianca Kollhorst,<sup>3</sup> Tania Schink,<sup>3</sup> Edeltraut Garbe,<sup>3</sup> Ron Herings,<sup>4</sup> Huub Straatman,<sup>4</sup> René Schade,<sup>5</sup> Marco Villa,<sup>6</sup> Silvia Lucchi,<sup>6</sup> Vera Valkhoff,<sup>5</sup> Silvana Romio,<sup>5</sup> Frantz Thiessard,<sup>7</sup> Martijn Schuemie,<sup>5</sup> Antoine Pariente,<sup>7</sup> Miriam Sturkenboom,<sup>5</sup> Giovanni Corrao<sup>1</sup> On behalf of the Safety of Non-steroidal Anti-inflammatory Drugs (SOS) Project Consortium

**Setting:** Five population based healthcare databases from four European countries (The Netherlands, Italy, Germany, UK).

**Participants:** Adult individuals (age  $\geq 18$  years) who started NSAID treatment in 2000-10. Overall, 92 163 hospital admissions for heart failure were identified and matched with 8 246 403 controls.



# Associations between current use of individual NSAIDs and risk of hospital admission for heart failure



\*past use of any NSAID as reference.

## RESEARCH

---

### 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

 OPEN ACCESS

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

**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)

**Lapi F et al BMJ 2013; 346: e8525**

# Relation of Nonsteroidal Anti-inflammatory Drugs to Serious Bleeding and Thromboembolism Risk in Patients With Atrial Fibrillation Receiving Antithrombotic Therapy

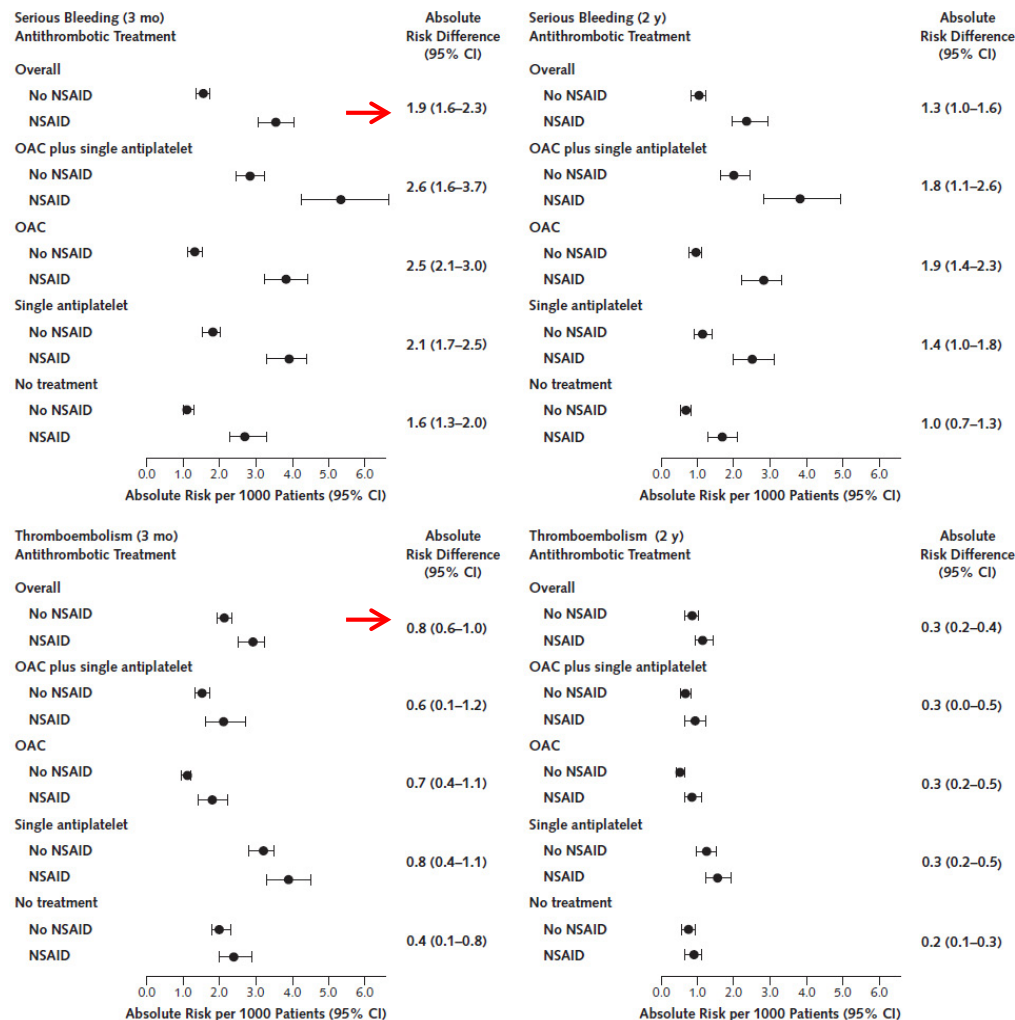
## A Nationwide Cohort Study

Morten Lamberts, MD, PhD; Gregory Y.H. Lip, MD\*; Morten Lock Hansen, MD, PhD; Jesper Lindhardsen, MD, PhD; Jonas Bjerring Olesen, MD, PhD; Jakob Raunsø, MD, PhD; Anne-Marie Schjerning Olsen, MD, PhD; Per Kragh Andersen, PhD, DMSc; Thomas Alexander Gerds, Dr Rer Nat; Emil L. Fosbøl, MD, PhD; Christian Torp-Pedersen, MD, DMSc\*; and Gunnar H. Gislason, MD, PhD\*

Ann Intern Med 2014;161:690–698

# Risks for serious bleeding and thromboembolism at 3 mo and 2 years with and without 14 d of NSAID exposure

Figure 1. Risks for serious bleeding and thromboembolism at 3 mo and 2 y, with and without 14 d of NSAID exposure.



Absolute risk differences were reported as NSAID exposure minus no NSAID exposure for each antithrombotic treatment group. The absolute risks were derived from Cox regression analysis, and 95% CIs were determined as quantiles of results in 200 bootstrap samples. "Single antiplatelet" denotes aspirin or clopidogrel. NSAID = nonsteroidal anti-inflammatory drug; OAC = oral anticoagulant.



# Meta-Analysis of Nonsteroidal Anti-Inflammatory Drug Use and Risk of Atrial Fibrillation



Gang Liu, MD, PhD<sup>a</sup>, Yu-Peng Yan, MD<sup>b</sup>, Xin-Xin Zheng, MD, PhD<sup>a</sup>, Yan-Lu Xu, MD, PhD<sup>a</sup>,  
Jie Lu, MD<sup>a</sup>, Ru-Tai Hui, MD, PhD<sup>b</sup>, and Xiao-Hong Huang, MD, PhD<sup>a,\*</sup>

**Meta-analysis with >400 000 cases of atrial fibrillation.**

**Am J Cardiol 2014;114:1523-1529**

# Evidence on NSAIDs use in relation to atrial fibrillation

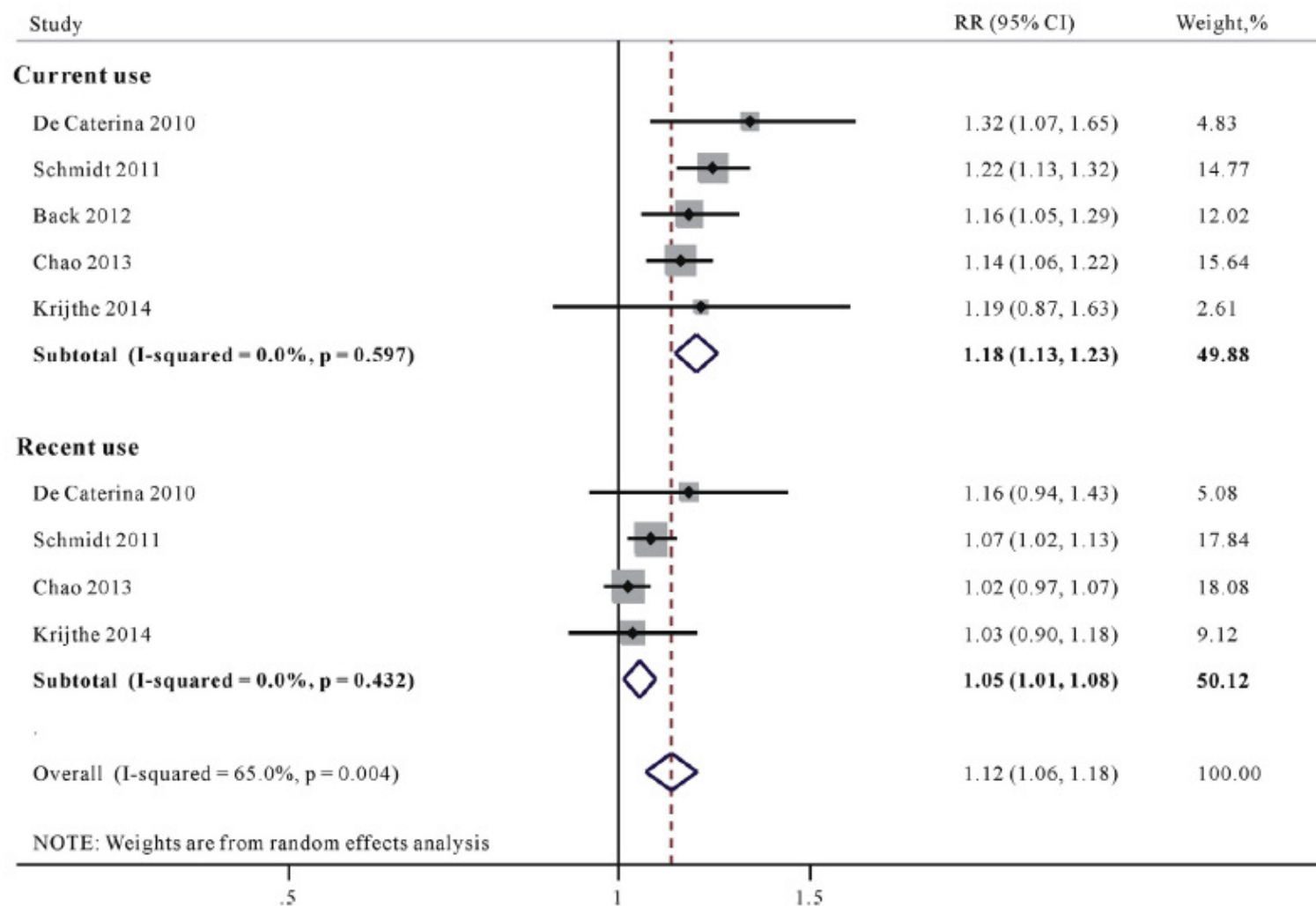
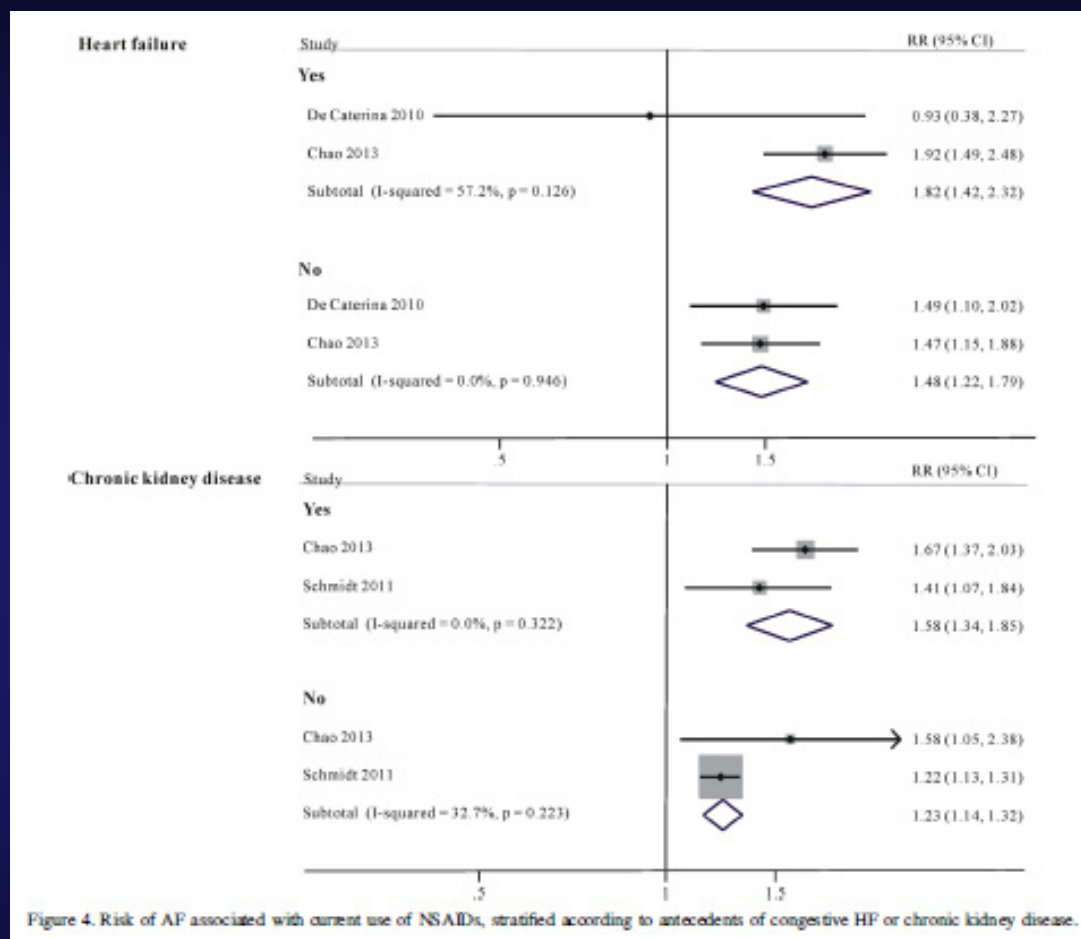


Figure 2. Combined estimate of RR and 95% CI of nonaspirin NSAIDs associated with risk of AF. Subgroup analyses were also performed when the exposure to NSAIDs was categorized as current and recent use.

# Evidence on NSAIDs use in relation to atrial fibrillation



Sub-groups of patients with a particular high risk were patients with heart failure (RR = 1.82, 95% CI: 1.42–2.32) and chronic kidney disease (1.58, 1.34–1.85).

# **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,<sup>a</sup> Thomas H. Wang, MD,<sup>a</sup> Lisa Wisniewski, RN,<sup>a</sup> Kathy Wolski, MPH,<sup>a</sup> Peter Libby, MD,<sup>b</sup> Thomas F. Lüscher, MD,<sup>c</sup> Jeffrey S. Borer, MD,<sup>d</sup> Alice M. Mascette, MD,<sup>c</sup> M. Elaine Husni, MD, MPH,<sup>f</sup> Daniel H. Solomon, MD, MPH,<sup>g</sup> David Y. Graham, MD,<sup>h</sup> Neville D. Yeomans, MD,<sup>i</sup> Henry Krum, MBBS, PhD, FRACP,<sup>j</sup> Frank Ruschitzka, MD,<sup>c</sup> A. Michael Lincoff, MD,<sup>a</sup> and Steven E. Nissen, MD<sup>a</sup> for the PRECISION Investigators  
*Cleveland, OH; Boston, MA; Zurich, Switzerland; New York, NY; Bethesda, MD; Houston, TX; and Sydney and Melbourne, Australia*

**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.**







# Take Home Messages

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- Prescription of non-aspirin NSAIDs requires in each particular case a careful evaluation of the risk of cardiovascular complications and bleeding (individualized assessment of both gastrointestinal and cardiovascular risk)
- **Non-aspirin NSAIDs should only be sold over the counter when measures are put in place to ensure that their use is accompanied by an appropriate warning of their frequent cardiovascular complications.**
- The patient should be encouraged to use these drugs when required and at the minimally effective dose rather than as a standing dose.

# Take Home Messages

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- Non-aspirin NSAIDs should not be used in patients with established or at high risk of cardiovascular disease.
- When prescribing traditional NSAIDs, older selective COX-2 inhibitors such as diclofenac, should be avoided, as no available data demonstrate a therapeutic superiority compared with other agents that justify their use in view of their associated cardiovascular risks.

# Take Home Messages

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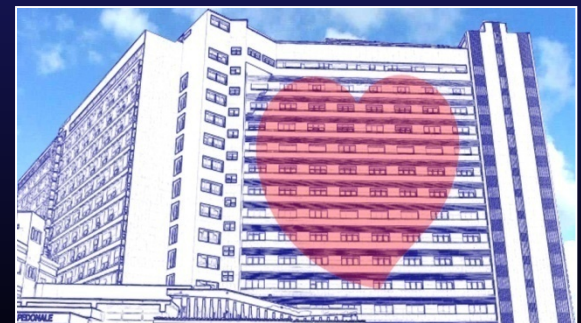
# NSAIDs and Cardiovascular Risk

## Non-aspirin non-steroidal anti-inflammatory drugs and cardiovascular risk

### ADVANCES IN CARDIAC ARRHYTHMIAS and GREAT INNOVATIONS IN CARDIOLOGY

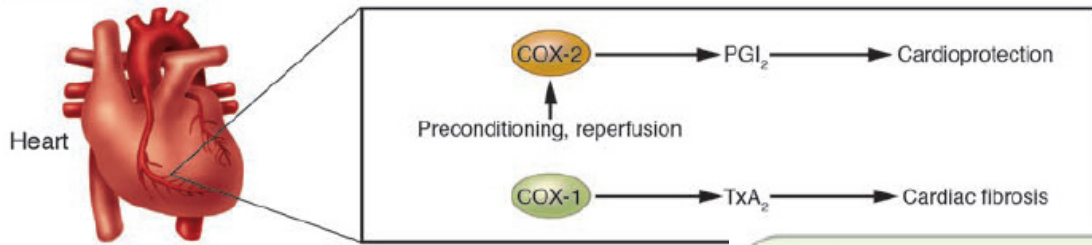
Turin October 13-15, 2016  
Centro Congressi Unione Industriale di Torino

Giuseppe Di Pasquale  
Direttore Dipartimento Medico ASL Bologna  
Direttore Unità Operativa Cardiologia  
Ospedale Maggiore, Bologna



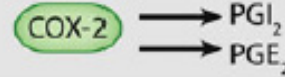
# Roles of the COX isozymes in cardiovascular and renal biology

## C Cardioprotection



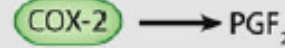
### Heart

Cardiomyocytes



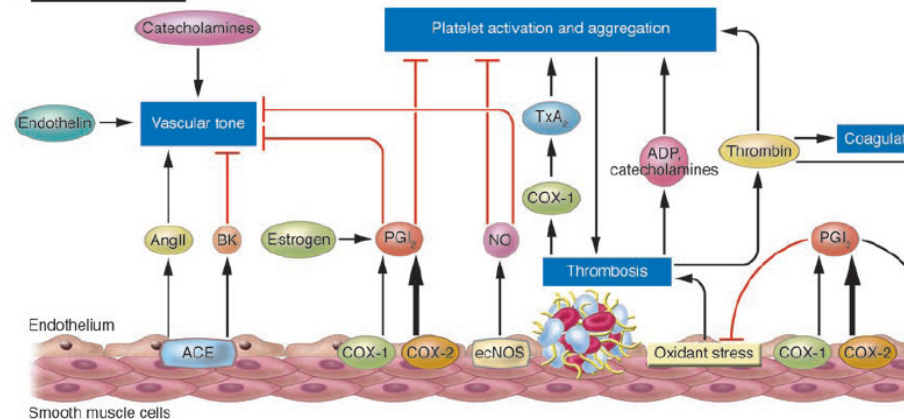
Ischemic preconditioning  
Protection against oxidative injury  
Antiarrhythmic activity

Fibroblasts



Fibrosis  
arrhythmia

## A Vascular function



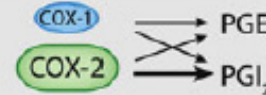
### Vasculature

Platelets



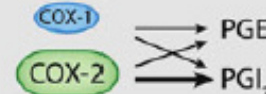
Platelet activation  
Vasoconstriction

Endothelium



Platelet inhibition  
Induction of thrombomodulin  
Protection against oxidative injury  
Antiadhesion

Smooth muscle



Platelet inhibition  
Induction of thrombomodulin  
Protection against oxidative injury  
Vasodilation

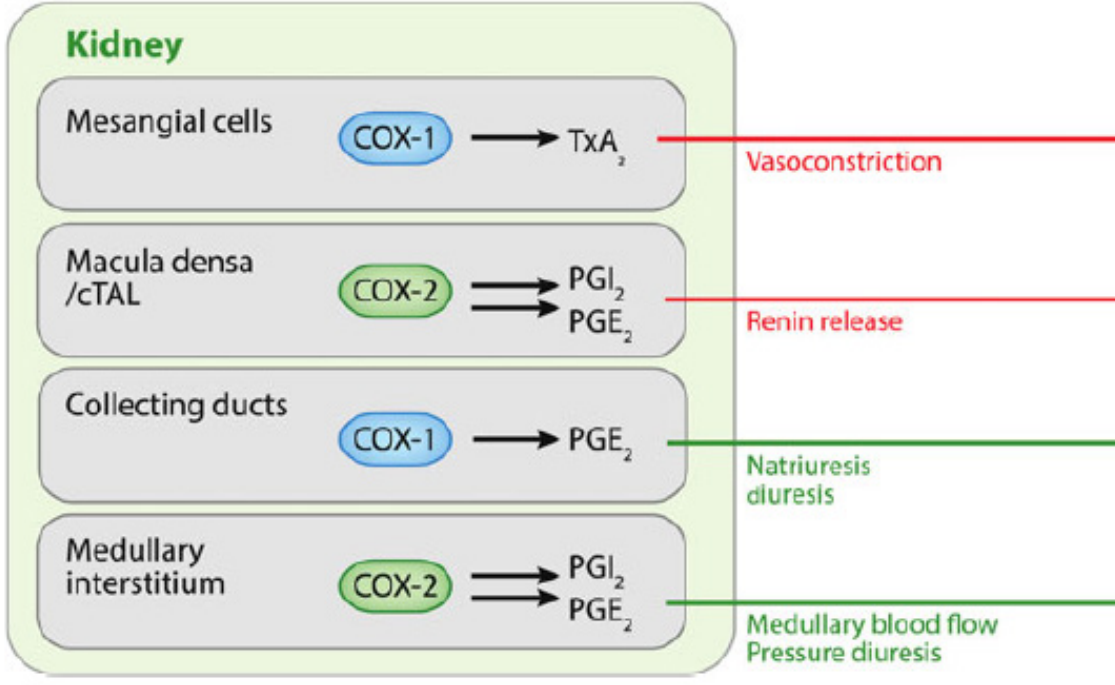
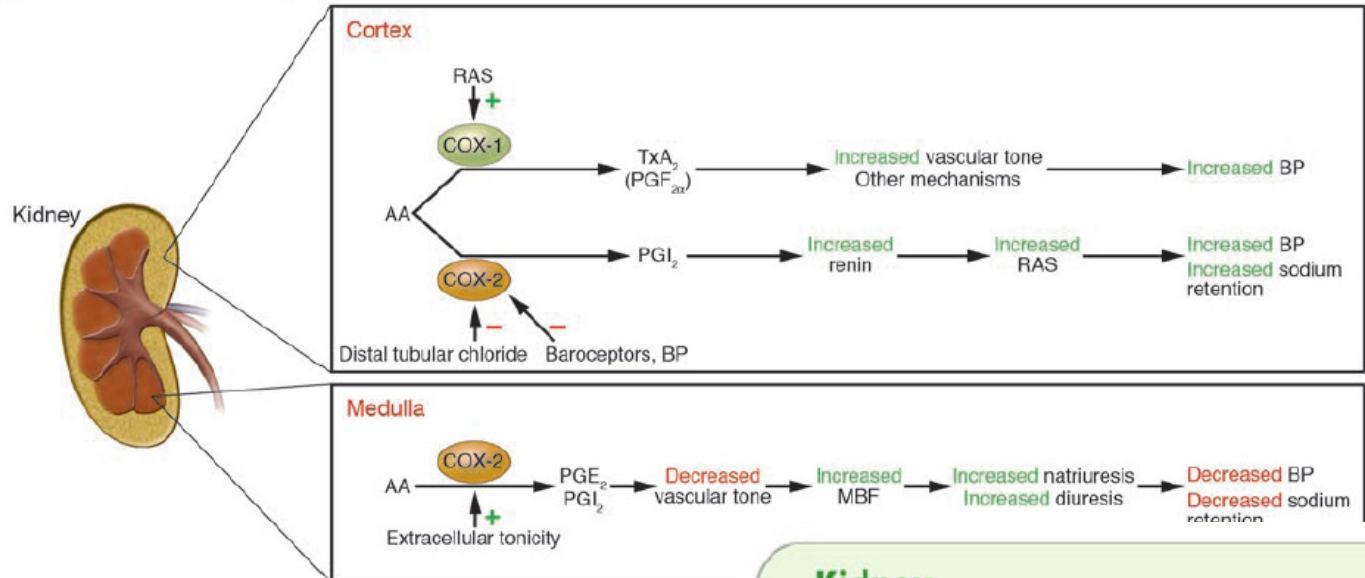
Macrophages



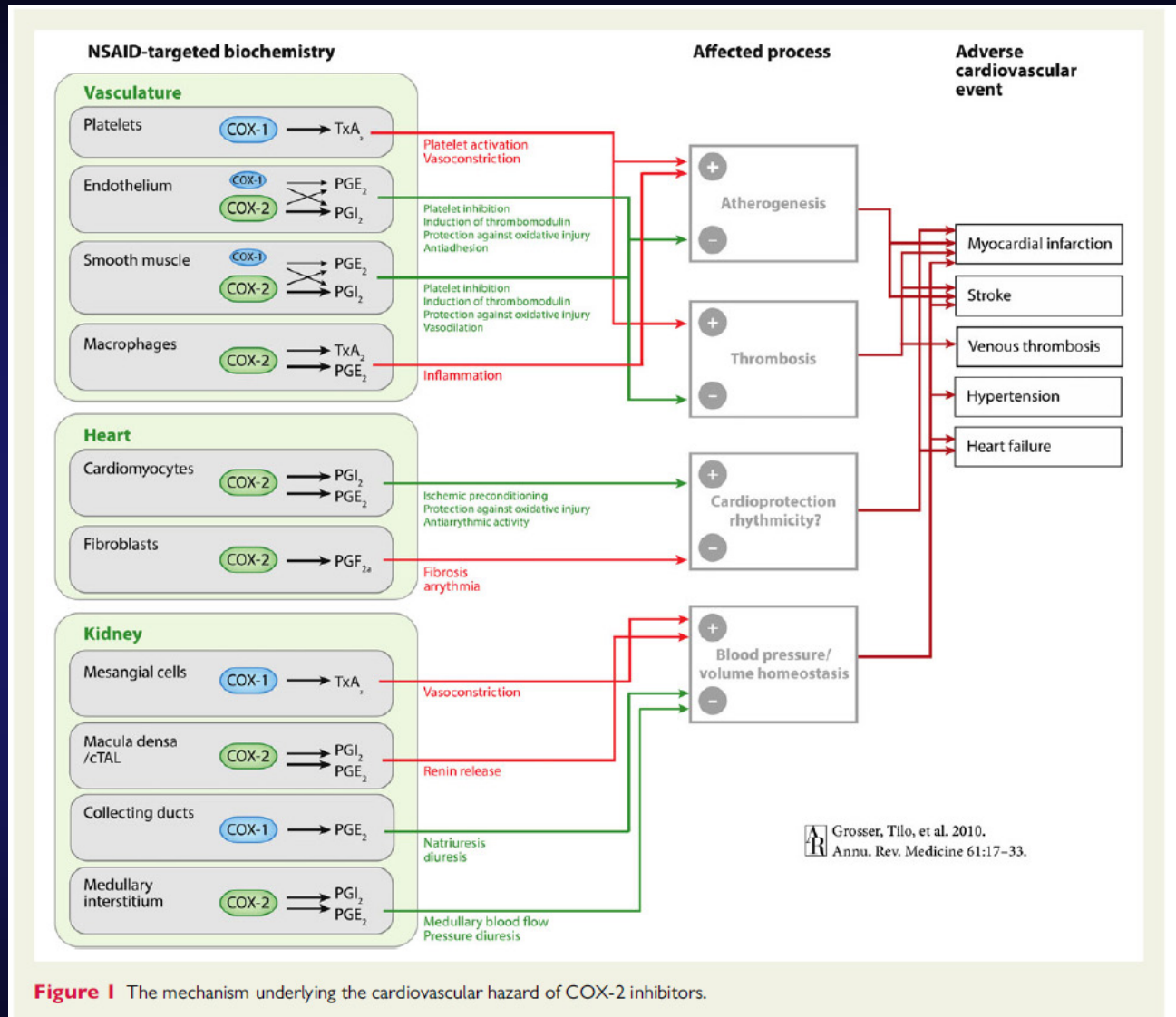
Inflammation

# Roles of the COX isozymes in cardiovascular and renal biology

## B Blood pressure regulation



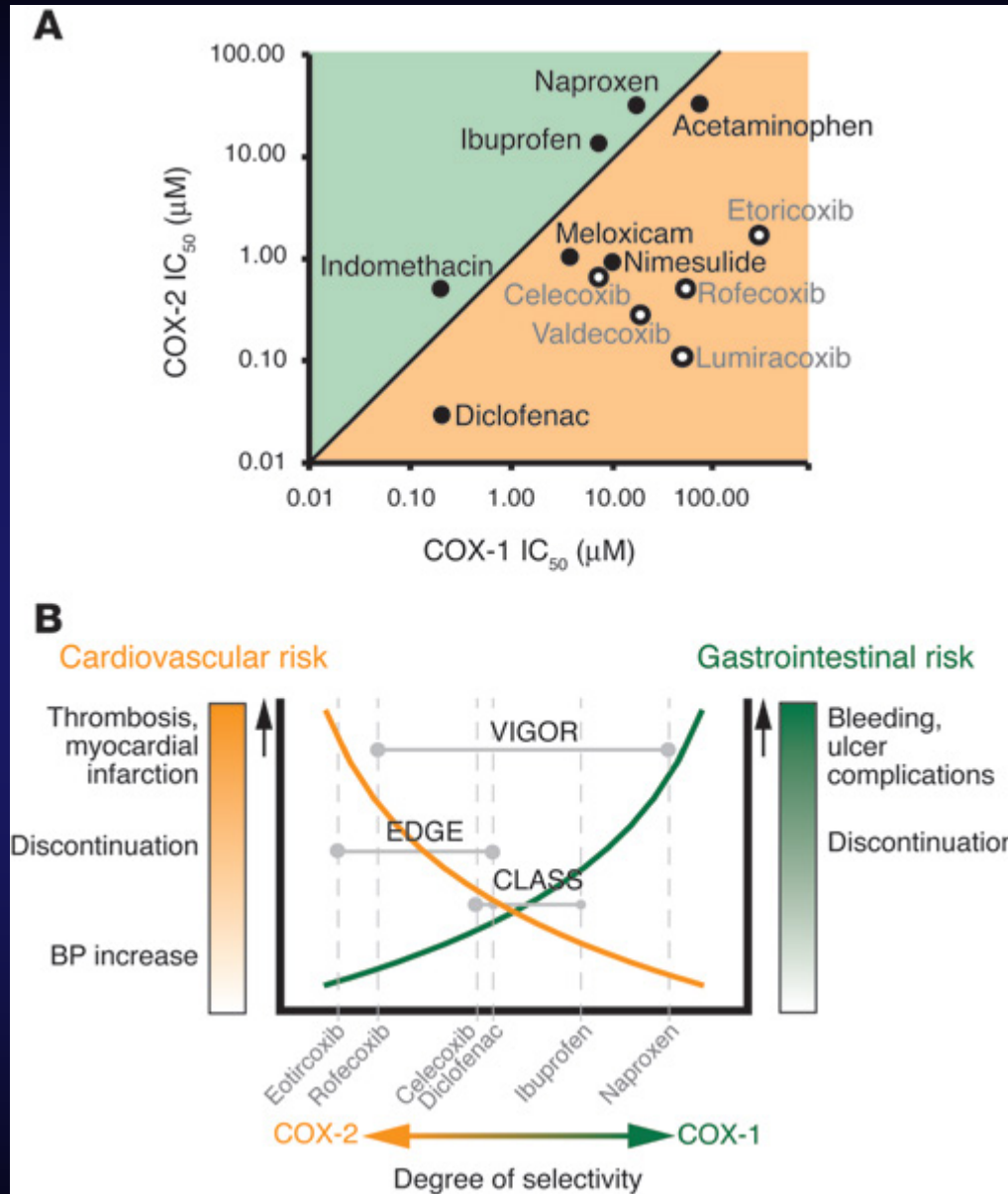
# Mechanisms and factors contributing to the cardiovascular toxicity



**Figure 1** The mechanism underlying the cardiovascular hazard of COX-2 inhibitors.



# Mechanism and factors contributing to the cardiovascular toxicity



Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest* 2006;116:4–15

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

Robert S. Bresalier, M.D., Robert James A. Bolognese, M.Stat., Bettina Christopher Lines, Ph.D., Robert Angel Lanas, M.D., Marvin A. Konik for the Adenomatous Polyp Prevention

The New England Journal of Medicine

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

CLAIRE ROMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D., HOCHBERG, M.D., TORE K. KVIEN, M.D., FOR THE VIGOR STUDY GROUP

### Hypertension

## Effect of Celecoxib on Cardiovascular Events and Blood Pressure in Two Trials for the Prevention of Colorectal Adenomas

Scott D. Solomon, MD; Marc A. Pfeffer, MD, PhD; John J.V. McMurray, MD; Rob I Peter Finn, MD; Bernard Levin, MD; Craig Eagle, MD; Ernest Hawk, MD; Marijosé I Ann G. Zauber, PhD; Monica M. Bertagnolli, MD; Nadir Arber, MD; Janet Witte for the APC and PreSAP Trial Investigators

VIGOR Study Group. N Engl J Med 2000;343:1520-1528

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib after Cardiac Surgery

Nancy A. Nussmeier, M.D., Andrew A. Whelton, M.D., Mark T. Brown, M.D., Richard M. Langford, F.R.C.A., Andreas Hoefft, M.D., Joel L. Parlow, M.D., Steven W. Boyce, M.D., and Kenneth M. Verburg, Ph.D.

Solomon SD, Circulation 2006;114:1028-1035

Nussmeier NAN, Engl J Med 2005;352:1081-1091

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk



Establishing the degree of risk and the relative safety profiles between individual drugs is difficult because of clinical trial heterogeneity and a lack of randomized controlled trial data for older NSAIDs.

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk



Concerns regarding coxibs atherothrombotic complications have, however, raised reservations regarding their use and as a consequence, patients with rheumatic disease are often denied these medications inappropriately.

Paradoxically, an older and relatively selective COX-2 inhibitor, diclofenac, continues to be one of the most widely used drugs worldwide and is in most countries sold over the counter (despite the increasing evidence implying that the cardiovascular risks are comparable with that of coxibs).

Mixed COX-1/COX-2 inhibitors such as ibuprofen and naproxen are also used widely and, without solid evidence, assumed to be safe.

Moreover in contrast to guideline recommendations a surprisingly large proportion (35%) of patients with MI or CHF receive non-aspirin NSAIDs after discharge

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk Evidence from major randomized controlled trials

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. KVIEEN, M.D.,  
AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

Design, setting, period, and population	Exposures and outcomes (primary/secondary)	Results (95% CI) and limitations
RCT (double-blinded, active control)  22 countries (301 centres)  1999  RA patients (n = 8076)	Rofecoxib (50 mg/d) vs. naproxen (500 mg b.i.d.)  GI events/MI, MACE (thrombotic CV events)	GI event rate was 2.1 for rofecoxib vs. 4.5 for naproxen per 100 PY (HR 0.5, 0.3–0.6)  <b>Corresponding MI risk was 0.4 vs. 0.1%. The MI rate was 5-fold increased for rofecoxib (20 vs. 4 events) yielding an HR for MACE of 2.38 (1.39–4.00)</b>  Few events, not powered for safety, not placebo controlled

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

## Evidence from major randomized controlled trials

**The Celecoxib Long-term Arthritis Safety Study (CLASS):** tested the gastrointestinal toxicity of celecoxib compared with the traditional NSAIDs ibuprofen and diclofenac.

Design, setting, period, and population	Exposures and outcomes (primary/secondary)	Results (95% CI) and limitations
RCT (double-blinded, active controls) USA and Canada (386 centres) 1998–2000 OA or RA patients (≥18 years) (n = 8059)	Celecoxib (400 mg b.i.d.) vs. ibuprofen (800 mg t.i.d.) or diclofenac (75 mg b.i.d.)  GI events/MACE (MI, stroke, death)	No difference in risk of GI events or MACE (0.9% for celecoxib vs. 1.0% for ibuprofen/diclofenac)  Few events, not powered for safety, not placebo-controlled

**Re-analyses of CLASS found no difference in gastrointestinal toxicity and a similar cardiovascular event rate for the three drugs.**

**A pooled analysis of VIGOR and CLASS found that compared with a matched non-treatment group, celecoxib and rofecoxib carried an increased cardiovascular risk.**



# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

## Evidence from major randomized controlled trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

Robert S. Bresalier, M.D., Robert S. Sandler, M.D., Hui Quan, Ph.D., James A. Bolognese, M.Stat., Bettina Oxenius, M.D., Kevin Horgan, M.D., Christopher Lines, Ph.D., Robert Riddell, M.D., Dion Morton, M.D., Angel Lanas, M.D., Marvin A. Konstam, M.D., and John A. Baron, M.D., for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators\*

Design, setting, period, and population	Exposures and outcomes (primary/secondary)	Results (95% CI) and limitations
<p>RCT (double-blinded, placebo-controlled)</p> <p>29 countries (108 centres)</p> <p>2000–2001</p> <p>Colorectal adenoma patients (n = 2586)</p>	<p>Rofecoxib (25 mg/d) vs placebo</p> <p>MACE (MI, unstable angina, cardiac death, ischaemic stroke, TCI, peripheral arterial thrombosis, DVT, pulmonary embolism)</p>	<p>Rate of MACE was 1.50 for rofecoxib and 0.78 for placebo per 100 PY, yielding HRs of 1.92 (1.19–3.11) for MACE, 2.80 (1.44–5.45) for cardiac events, and 2.32 (0.89–6.74) for cerebrovascular events.</p> <p>All-cause and CV death rates were similar</p> <p>Relatively few events</p>

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

## Evidence from major randomized controlled trials

**Table 2.** Incidence of Adjudicated Thrombotic Adverse Events.\*

Adverse Event	Rofecoxib Group (N=1287)		Placebo Group (N=1299)		Hazard Ratio (95% CI)
	No. of Patients (%)	Rate/100 Patient-yr	No. of Patients (%)	Rate/100 Patient-yr	
<b>Total</b>	46 (3.6)	1.50	26 (2.0)	0.78	1.92 (1.19–3.11)
<b>Cardiac events</b>	31 (2.4)	1.01	12 (0.9)	0.36	2.80 (1.44–5.45)
Myocardial infarction	21		9		
Fatal myocardial infarction	2		3		
Sudden death from cardiac causes	3		1		
Unstable angina pectoris	7		4		
<b>Cerebrovascular events</b>	15 (1.2)	0.49	7 (0.5)	0.21	2.32 (0.89–6.74)
Fatal ischemic stroke	1		0		
Ischemic stroke	11		6		
Transient ischemic attack	5		2		
<b>Peripheral vascular events</b>	3 (0.2)	0.10	7 (0.5)	0.21	0.46 (0.08–2.03)
Peripheral arterial thrombosis	1		1		
Peripheral venous thrombosis	2		4		
Pulmonary embolism	0		2		

Evidence from major randomized controlled trials

The **NEW ENGLAND**  
**JOURNAL of MEDICINE**

ESTABLISHED IN 1812

MARCH 17, 2005

VOL. 352 NO. 11

## Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention

Scott D. Solomon, M.D., John J.V. McMurray, M.D., Marc A. Pfeffer, M.D., Ph.D., Janet Wittes, Ph.D., Robert Fowler, M.S., Peter Finn, M.D., William F. Anderson, M.D., M.P.H., Ann Zauber, Ph.D., Ernest Hawk, M.D., M.P.H., and Monica Bertagnolli, M.D., for the Adenoma Prevention with Celecoxib (APC) Study Investigators\*

Design, setting, period, and population	Exposures and outcomes (primary/secondary)	Results (95% CI) and limitations
RCT (double-blinded, placebo-controlled) US, UK, Australia, Canada (91 centres) 1999–2002 Colorectal neoplasia patients (n = 2035)	Celecoxib (200 or 400 mg b.i.d.) vs. placebo  MACE (MI, stroke, CV death, HF)	Risk of MACE was 1% for placebo, 2.3% for 200 mg celecoxib b.i.d. (HR 2.3, 0.9–5.5), and 3.4% for 400 mg celecoxib b.i.d. (HR 3.4, 1.4–7.8)  Few events, not powered for safety

The Adenoma Prevention with Celecoxib (APC) study showed increased vascular risks associated with celecoxib use.

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

Evidence from major randomized controlled trials

## Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison

*Christopher P Cannon, Sean P Curtis, Garret A FitzGerald, Henry Krum, Amarjot Kaur, James A Bolognese, Alise S Reicin, Claire Bombardier, Michael E Weinblatt, Désirée van der Heijde, Erland Erdmann, Loren Laine, for the MEDAL Steering Committee\**

Design, setting, period, and population	Exposures and outcomes (primary/secondary)	Results (95% CI) and limitations
<p>Pooled analysis of three double-blinded RCTs (MEDAL, EDGE, EDGE II)</p> <p>46 countries (1380 centres)</p> <p>2002–2006</p> <p>OA or RA patients</p> <p>(n = 34 701)</p>	<p>Etoricoxib (60 or 90 mg/d) vs. diclofenac (150 mg/d)</p> <p>MACE (thrombotic CV events)/GI events</p>	<p>MACE rate per 100 PY was 1.24 for etoricoxib and 1.30 diclofenac (HR 0.95, 0.81–1.11).</p> <p>Upper GI event rate was lower with etoricoxib vs. diclofenac (0.67 vs. 0.97; HR 0.69, 0.57–0.83), but similar for complicated upper GI events (0.30 vs. 0.32)</p>



## Cardiovascular and Cerebrovascular Events in the Randomized, Controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT)

ADAPT Research Group<sup>\*</sup>:

RCT (double-blinded, active, and placebo controls)  
US (6 centres)  
2001–2004  
AD patients  $\geq 70$  years  
( $n = 2528$ )

Celecoxib (200 mg b.i.d.) or naproxen (220 mg b.i.d.) vs. placebo  
MACE (MI, stroke, CV death, HF, and TCI)

**Table 3.** Incidences and Hazard Ratios for First Occurrence of Events by Treatment Group

		Celecoxib	Naproxen	Placebo						
Event	Subcategory (Number of Events)	Events (3-y Incidence) (%) <sup>a</sup>			Celecoxib vs. Placebo			Naproxen vs. Placebo		
		Celecoxib	Naproxen	Placebo	Hazard Ratio	95%CI	p-Value	Hazard Ratio	95%CI	p-Value
Number with follow-up data		717	713	1,070						
Cardio/cerebrovascular events	MI (34)	8 (1.80)	13 (2.19)	13 (2.01)	0.91	0.38–2.19	0.83	1.49	0.69–3.22	0.31
	Stroke (24)	7 (1.05)	10 (2.38)	7 (1.23)	1.47	0.52–4.20	0.47	2.13	0.81–5.60	0.12
	CHF (18)	3 (0.73)	8 (1.51)	7 (0.85)	0.63	0.16–2.44	0.50	1.70	0.62–4.69	0.30
	TIA (27)	8 (1.55)	9 (2.20)	10 (1.35)	1.08	0.42–2.78	0.87	1.34	0.55–3.31	0.52
Composite events	CV death/MI (39)	11 (2.41)	13 (2.19)	15 (2.52)	1.08	0.50–2.36	0.84	1.29	0.61–2.72	0.50
	CV death/MI/stroke (62)	17 (3.26)	23 (4.54)	22 (3.74)	1.14	0.61–2.15	0.68	1.57	0.87–2.81	0.13
	CV death/MI/stroke/ CHF (79)	20 (4.00)	31 (6.05)	28 (4.46)	1.06	0.60–1.88	0.85	1.66	1.00–2.77	0.05
	CV death/MI/stroke/ CHF/ TIA (105)	28 (5.54)	40 (8.25)	37 (5.68)	1.10	0.67–1.79	0.72	1.63	1.04–2.55	0.03
Aspirin	Aspirin use at baseline (45)	14 (8.40)	15 (9.58)	16 (7.55)	1.24	0.60–2.58	0.56	1.40	0.69–2.83	0.35
	No aspirin use at baseline (60)	14 (4.30)	25 (7.87)	21 (4.87)	0.98	0.50–1.92	0.95	1.81	1.01–3.24	0.04

Hazard ratios, CIs, and *p*-values were obtained using Cox proportional hazards regression of the first occurrence of events.

<sup>a</sup> 3-y incidence is the percentage of participants experiencing the event by 3 y after randomization, as estimated with the Kaplan-Meier method.

doi:10.1371/journal.pctr.0010033.t003

PLoS Clin Trials 2006;1:e33

3-year risk of MACE in the celecoxib, naproxen, and placebo-treated groups were 5.54% (28/717), 8.25% (40/713), and 5.68% (37/1070). Hazard ratio for MACE was 1.10 (0.67–1.79) for celecoxib and 1.63 (1.04–2.55) for naproxen compared with placebo  
Few events.

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

Evidence from major randomized controlled trials

## EXTENDED REPORT

### Cardiovascular outcomes in high risk patients with osteoarthritis treated with ibuprofen, naproxen or lumiracoxib

M E Farkouh, J D Greenberg, R V Jeger, K Ramanathan, F W A Verheugt, J H Chesebro, H Kirshner,

Design, setting, period, and population	Exposures and outcomes (primary/secondary)	Results (95% CI) and limitations
<p>RCT (double-blinded, active controls)</p> <p>29 countries (849 centres)</p> <p>2001–2002</p> <p>OA patients (n = 18 325)</p>	<p>Lumiracoxib (400 mg/d) vs. ibuprofen (800 mg t.i.d.) (sub-study 1) or naproxen (500 mg b.i.d.) (sub-study 2)</p> <p>MACE (MI, stroke, CV death)/HF</p>	<p>In high-risk patients using aspirin (75–100 mg/d), MACE risk was higher for ibuprofen (2.14%) vs. lumiracoxib (0.25%) (P = 0.038), but similar for naproxen (1.58%) and lumiracoxib (1.48%).</p> <p><b>In high-risk patients not using aspirin, MACE risk was lower for naproxen (0%) than lumiracoxib (1.57%) (P = 0.027), but not ibuprofen vs. lumiracoxib (0.92 vs. 0.80%).</b></p> <p>Heart failure risk was higher for ibuprofen than lumiracoxib (1.28 vs. 0.14%; P = 0.031), but similar for naproxen and lumiracoxib.</p> <p>Post hoc analysis, not placebo controlled, stratification on aspirin/CV risk not pre-planned</p>

No difference in cardiovascular risk between lumiracoxib and ibuprofen or naproxen.



# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

Evidence from major randomized controlled trials

**Table 2** Incidence of the composite cardiovascular outcome by baseline risk

	Without aspirin		HR (95% CI)	p Value	With aspirin		HR (95% CI)	p Value
	Ibuprofen No (%)	Lumiracoxib No (%)			Ibuprofen No (%)	Lumiracoxib No (%)		
<i>Ibuprofen substudy</i>								
Overall	13/3431 (0.38)	13/3401 (0.38)	1.06 (0.49 to 2.28)	0.88	10/966 (1.04)	6/975 (0.62)	1.79 (0.65 to 4.93)	0.26
Low CV risk	11/3181 (0.35)	10/3075 (0.33)	1.13 (0.48 to 2.66)	0.77	2/593 (0.34)	5/581 (0.86)	0.40 (0.08 to 2.08)	0.27
High CV risk	2/250 (0.80)	3/326 (0.92)	0.91 (0.15 to 5.47)	0.92	8/373 (2.14)	1/394 (0.25)	9.08 (1.13 to 72.76)	0.038
<i>Naproxen substudy</i>								
Overall	14/3537 (0.40)	22/3549 (0.62)	0.67 (0.34 to 1.31)	0.242	13/1193 (1.09)	18/1192 (1.51)	0.70 (0.35 to 1.44)	0.337
Low CV risk	14/3202 (0.44)	17/3231 (0.53)	0.88 (0.43 to 1.78)	0.714	5/688 (0.73)	10/651 (1.54)	0.45 (0.15 to 1.32)	0.149
High CV risk	0/335 (0.00)	5/318 (1.57)	Not applicable	0.027*	8/505 (1.58)	8/541 (1.48)	1.07 (0.40 to 2.84)	0.899

In high-risk patients using aspirin (75–100 mg/d), MACE risk was higher for ibuprofen (2.14%) vs. lumiracoxib (0.25%) ( $P = 0.038$ ), but similar for naproxen (1.58%) and lumiracoxib (1.48%).

In high-risk patients not using aspirin, MACE risk was lower for naproxen (0%) than lumiracoxib (1.57%) ( $P = 0.027$ ), but not ibuprofen vs. lumiracoxib (0.92 vs. 0.80%).

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

Evidence from major randomized controlled trials

It is evident that relatively few major trials have been conducted and most of these were not designed specifically to answer whether coxibs carry an increased thromboembolic risk

*The post hoc analyses from the various trials raise a clear warning sign concerning the cardiovascular risk associated with use of selective COX-2 inhibitors in general*

Most randomized trials were conducted in different patient populations, age groups, and treatment settings

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

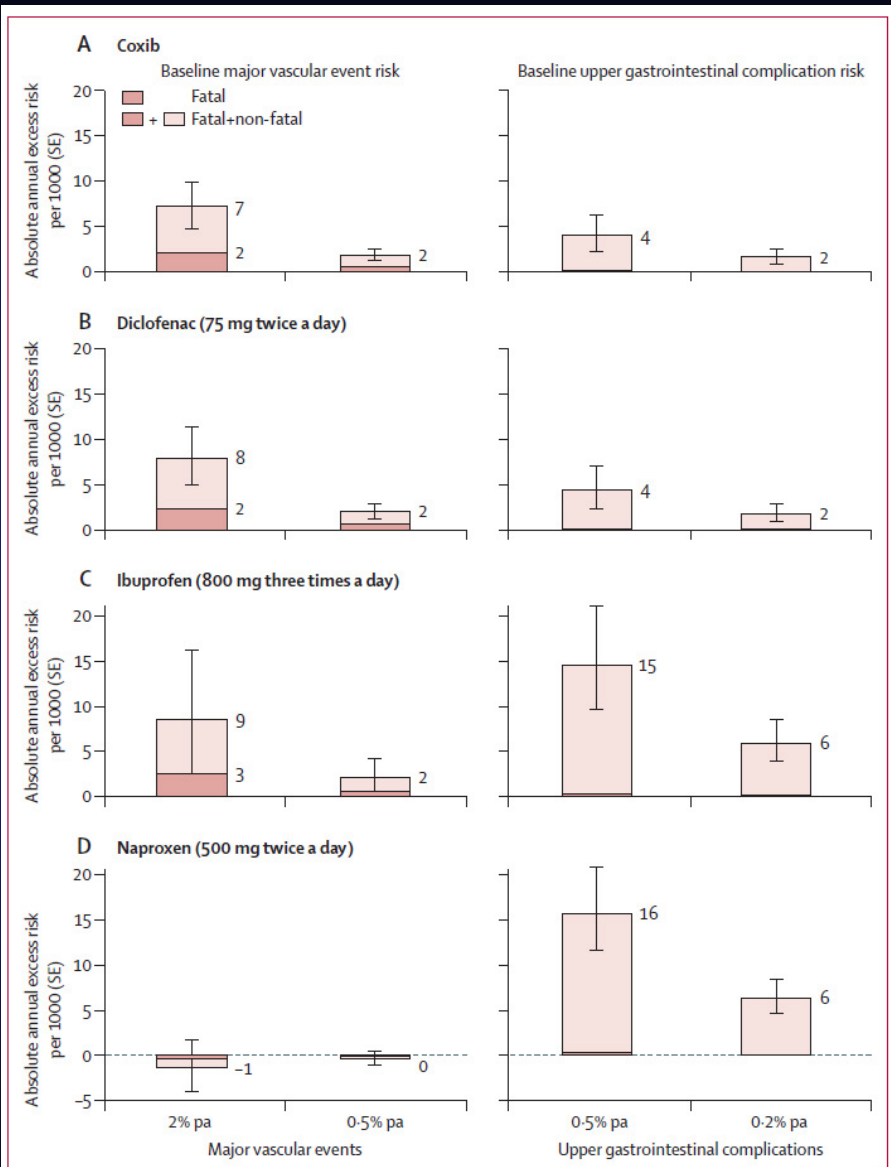


Figure 5: Annual absolute effects per 1000 of coxibs and tNSAIDs at different baseline risks of major vascular events and upper gastrointestinal complications

The vascular risks of diclofenac (RR = 1.41, 95% CI: 1.12–1.78), and possibly high-dose ibuprofen (1.44, 0.89–2.33), were comparable with coxibs (1.37, 1.14–1.66)

The increased vascular risk was driven by an increased rate of major coronary events and were independent of baseline characteristics, including cardiovascular risk

In contrast, naproxen did not increase the risk of major vascular events (0.93, 0.69–1.27)

Finally, all non-aspirin NSAIDs roughly doubled the risk of heart failure

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk Evidence from observational studies

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PLOS MEDICINE

## Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies

Patricia McGettigan<sup>1</sup>, David Henry<sup>2,3,4\*</sup>

<sup>1</sup>Hull York Medical School, Hull, United Kingdom, <sup>2</sup>Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada, <sup>3</sup>Department of Medicine, University of Toronto, Toronto, Ontario, Canada, <sup>4</sup>Discipline of Clinical Pharmacology, School of Medicine and Public Health, University of Newcastle, Newcastle, Australia

Data from 21 cohort studies with > 2.7 million exposed individuals and 30 case–control with a total of 184 946 cardiovascular events.

For ibuprofen, a cardiovascular risk was seen only with the use of higher doses (1200 mg/day).

Naproxen was risk-neutral at all doses, and had also a lower risk when compared directly with ibuprofen (0.92, 0.87–0.99).

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

## Evidence from observational studies

**Table 1.** Summary of the numbers of studies and overall results.

Drug	Case-Control Studies		Cohort Studies		Total Number of Studies	Pooled RR (95% CI)	Heterogeneity		
	Number of Studies	Number of Exposed Cases/ Controls	Number of Studies	Number of Person-Years of Exposure			Cochran Q	p-Value	I <sup>2</sup>
Naproxen	24	3,103/24,468	17	159,824	41	1.09 (1.02, 1.16)	143.1	<0.0001	70.70%
Ibuprofen	21	5,716/37,207	17	255,621	38	1.18 (1.11, 1.25)	226.7	<0.0001	81.90%
Celecoxib	20	1,496/12,755	15	179,479	35	1.17 (1.08, 1.27)	236.9	<0.0001	84.40%
Rofecoxib	19	1,662/10,827	15	126,219	34	1.45 (1.33, 1.59)	227.8	<0.0001	84.20%
Diclofenac	16	3,181/13,523	13	50,736	29	1.40 (1.27, 1.55)	224.4	<0.0001	86.60%
Indomethacin	11	788/4,406	3	9,350	14	1.30 (1.19, 1.41)	20.8	0.1	32.60%
Piroxicam	7	288/1,216	1	0 <sup>a</sup>	8	1.08 (0.91, 1.30)	8.6	0.3	18.90%
Meloxicam	6	240/714	1	0 <sup>a</sup>	7	1.20 (1.07, 1.33)	2.8	0.7	0%
Etodolac	4	464/4,115	1	8,994	5	1.55 (1.28, 1.87)	18.9	0.01	57.70%
Etoricoxib	4	60/116	0	0	4	2.05 (1.45, 2.88)	0.7	0.9	0%
Valdecoxib	1	2/2	4	5,629	5	1.05 (0.81, 1.36)	13.4	0.004	77.60%

<sup>a</sup>Studies reporting adjusted risk estimates did not all report person-years of exposure.

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The highest overall cardiovascular risk was observed for rofecoxib (RR = 1.45, 95% CI: 1.33–1.59) and diclofenac (1.40, 1.27–1.55) and the lowest for ibuprofen (1.18, 1.11–1.25) and naproxen (1.09, 1.02–1.16).

The risk was elevated even with low doses of rofecoxib (1.37, 1.20–1.57), celecoxib (1.26, 1.09–1.47), and diclofenac (1.22, 1.12–1.33), and rose in each case with the use of higher doses.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib after Cardiac Surgery

Nancy A. Nussmeier, M.D., Andrew A. Whelton, M.D., Mark T. Brown, M.D.,  
Richard M. L. Ste

#### CONCLUSIONS

The use of parecoxib and valdecoxib after CABG was associated with an increased incidence of cardiovascular events, arousing serious concern about the use of these drugs in such circumstances.

This randomized trial (n = 1671) showed that short-term use of coxibs (intravenous parecoxib for at least 3 days, followed by valdecoxib until day 10) were associated with an increased risk of cardiovascular events after coronary artery bypass grafting compared with standard care plus placebo (RR = 3.7, 95% CI: 1.0–13.5).



### Postoperative naproxen after coronary artery bypass surgery: a double-blind randomized controlled trial

Alexander Kulik<sup>a</sup>, Marc Ruel<sup>a,c</sup>, Michael E. Bourke<sup>b</sup>, Lynn Sawyer<sup>a</sup>, John Penning<sup>d</sup>,  
Howard J. Nathan<sup>b</sup>, Thierry G. Mesana<sup>a</sup>, Pierre Bédard<sup>a,\*</sup>

<sup>a</sup>*Division of Cardiac Surgery, University of Ottawa Heart Institute, Ottawa, Ont., Canada*

<sup>b</sup>*Division of Cardiac Anesthesia, University of Ottawa Heart Institute, Ottawa, Ont., Canada*

<sup>c</sup>*Department of Epidemiology, University of Ottawa, Ottawa, Ont., Canada*

<sup>d</sup>*Department of Anesthesiology, University of Ottawa, Ottawa, Ont., Canada*

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Randomized trial (n=98) found naproxen to be an effective adjunct for optimization of pain control, with no apparent increase in other complications.

Still, together with the risk-neutral effect reported in other patient groups the results of these trials indicate that naproxen may be the safest non-aspirin NSAID to use following cardiac surgery.

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

## Evidence on NSAIDs use in combination with antithrombotic treatment

In patients with venous thromboembolism, a study showed a 1.8-fold increased risk for clinically relevant bleeding and 2.4-fold increased risk for major bleeding in patients co-administered non-aspirin NSAIDs and anticoagulation with rivaroxaban or enoxaparin-vitamin K antagonist.

### Original Investigation

## Bleeding Risk of Patients With Acute Venous Thromboembolism Taking Nonsteroidal Anti-Inflammatory Drugs or Aspirin

Bruce L. Davidson, MD, MPH; Sara Verheijen, BS; Anthonie W. A. Lensing, MD, PhD; Martin Gebel, PhD; Timothy A. Brighton, MBBS; Roger M. Lyons, MD; Jeffrey Rehm, MD; Martin H. Prins, MD, PhD

# Non-aspirin Non-steroidal Anti-inflammatory Drugs and Cardiovascular Risk

## Evidence on NSAIDs use in relation to atrial fibrillation

Data from observational studies <NSAID-associated risk for atrial fibrillation> have been summarized in a recent meta-analysis with >400 000 cases of atrial fibrillation.

Compared with non-users, users of non-aspirin NSAIDs had a 1.2-fold increased risk of AF increasing to 1.5-fold among new users.

COX-2 inhibitors, particularly diclofenac, were associated with higher risks than non-selective NSAIDs.

Sub-groups of patients with a particular high risk were patients with heart failure (RR = 1.82, 95% CI: 1.42–2.32) and chronic kidney disease (1.58, 1.34–1.85).

## Conclusions

Prescription of non-aspirin NSAIDs requires in each particular case a careful evaluation of the risk of cardiovascular complications and bleeding (individualized assessment of both gastrointestinal and cardiovascular risk)

Non-aspirin NSAIDs should only be sold over the counter when measures are put in place to ensure that their use is accompanied by an appropriate warning of their frequent cardiovascular complications.

The patient should be encouraged to use these drugs when required and at the minimally effective dose rather than as a standing dose.

Non-aspirin NSAIDs should not be used in patients with established or at high risk of cardiovascular disease.

When prescribing traditional NSAIDs, older selective COX-2 inhibitors such as diclofenac, should be avoided, as no available data demonstrate a therapeutic superiority compared with other agents that justify their use in view of their associated cardiovascular risks.







