Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction

A Nationwide Cohort Study

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Background

- NSAIDs:
  - are commonly used
  - increased cardiovascular risk
    - @ in healthy individuals
    - @ established cardiovascular disease
- International guidelines discourage NSAID treatment in patients with established cardiovascular disease : MI,heart failure

Background

- little is known about the risk profile of each individual NSAID according to treatment duration or whether there is a safe treatment period for NSAIDs
- Treatment duration with COX-2 selective and nonselective NSAIDs like diclofenac, ibuprofen, and naproxen in patients with prior MI is absent

Method

- **Population and Data Sources**
- a population of all patients with first-time admission for MI from January 1, 1997, to December 31, 2006, in the Danish National Patient Registry (Denmark)
- First admission for MI implied that the National Patient Registry had not registered any prior admission for MI in the previous 19 years

Method

- All patients who were alive at discharge after their first-time MI were included in the study.
- Patients were censored at death or at the end of the study period (December 31, 2006).
- all claimed prescriptions of NSAIDs from the national prescription registry after discharge from index hospitalization (MI)

Method

- most commonly used
  - selective COX-2 inhibitors: rofecoxib and celecoxib,
  - nonselective NSAIDs: ibuprofen, diclofenac, and naproxen.
- **Statistics:**

  Unadjusted incidence rates of events per 1000 person-years for death and death/Re-MI were calculated for all NSAID treatment as a group and for the individual NSAIDs separately

Results

- A total of 102138 patients were admitted with first-time MI in the period of 1997 to 2006, of whom 83675 (81.9%) were discharged alive and included in the study.
- Mean±SD age in the population was 68±13.0 years; 63% were men.
- At least 1 prescription claim for NSAID treatment after discharge was identified for 35405 patients (42.3%) with prior MI.

Table. Baseline Characteristics of the Total Study Population and Individual Treatment Groups

Characteristic	Total Population, n (%)	No. NSAIDs, n (%)	Exposure Group, n (%)					
			Rofecoxib	Celecoxib	Ibuprofen	Diclofenac	Naproxen	Other NSAIDs
Total patients	83 677 (100.0)	48 270 (57.7)	3914 (4.7)	4000 (4.8)	19 377 (23.0)	11 181 (13.4)	1816 (2.2)	10 717 (12.8)
Mean±SD age, y	68.0±13.0	70.1±12.9	70.5±12.2	70.6±11.9	65.4±13.0	65.2±12.6	65.9±12.7	68.2±12.6
Women	31 011 (37.0)	17 978 (37.2)	1921 (49.0)	1988 (49.7)	6554 (33.8)	3692 (33.2)	570 (31.4)	4372 (40.8)
Men	52 666 (62.9)	30 292 (62.8)	1993 (50.9)	2012 (50.3)	12 823 (66.2)	7489 (67.0)	1246 (68.6)	6345 (59.2)
Comorbidity								
Cardiac arrhythmias	8903 (10.6)	5872 (12.2)	386 (9.9)	394 (9.9)	1482 (7.7)	860 (7.7)	135 (7.4)	920 (8.6)
Peripheral vascular disease	1480 (1.8)	934 (1.9)	59 (1.5)	77 (1.9)	283 (1.5)	146 (1.3)	25 (1.4)	166 (1.6)
Cerebral vascular disease	4302 (5.1)	2907 (6.0)	187 (4.8)	182 (4.6)	674 (3.5)	368 (3.3)	57 (3.1)	425 (4.0)
Diabetes mellitus with complications	3964 (4.7)	2463 (5.1)	169 (4.3)	173 (4.3)	848 (4.4)	434 (3.9)	70 (3.9)	384 (3.6)
Acute renal failure	820 (0.9)	617 (1.3)	27 (0.7)	19 (0.5)	97 (0.5)	42 (0.4)	7 (0.4)	53 (0.5)
Chronic renal failure	1120 (1.3)	841 (1.7)	30 (0.8)	27 (0.7)	141 (0.7)	62 (0.6)	14 (0.8)	65 (0.6)
Malignancy	495 (0.6)	334 (0.7)	13 (0.3)	18 (0.5)	81 (0.4)	52 (0.5)	6 (0.3)	38 (0.4)
Shock	995 (1.1)	652 (1.4)	40 (1.0)	31 (0.8)	131 (0.7)	90 (0.8)	21 (1.2)	83 (0.8)
COPD	969 (1.2)	650 (1.4)	34 (0.9)	32 (0.8)	152 (0.8)	84 (0.8)	20 (1.1)	110 (1.0)
Gastric ulcer	1461 (1.8)	897 (1.9)	94 (2.4)	90 (2.3)	235 (1.2)	145 (1.3)	26 (1.4)	180 (1.7)
Concomitant medical treatment								
β-blockers	58 141 (69.5)	32 496 (67.3)	2643 (67.5)	2741 (68.5)	14 366 (74.1)	8319 (74.1)	1291 (71.1)	7701 (71.9)
ACE inhibitors	34 890 (41.7)	20 548 (42.6)	1552 (39.7)	1620 (40.5)	7734 (39.9)	4466 (39.9)	718 (39.5)	4265 (39.8)
Statins	44 488 (53.2)	25 622 (53.1)	1594 (40.7)	1675 (41.9)	10 895 (56.2)	6163 (55.1)	901 (49.6)	5312 (49.6)
ASA	41 278 (49.3)	24 591 (50.9)	1503 (38.4)	1566 (39.2)	9340 (48.2)	5209 (46.6)	817 (44.9)	4826 (45.0)
Clopidogrel	29 395 (35.2)	18 532 (38.4)	696 (17.8)	842 (21.1)	6160 (31.8)	3317 (29.7)	449 (24.7)	2910 (27.2)
Spironolactone	7015 (8.4)	4414 (9.1)	320 (8.2)	368 (9.2)	1307 (6.8)	689 (6.2)	122 (6.7)	770 (7.2)
Loop diuretics	33 732 (40.3)	20 290 (42.0)	1820 (46.0)	1836 (45.9)	6798 (35.1)	3778 (33.8)	690 (38.0)	4304 (40.2)

Results

- There were 35257 death/MIs (42.1%) and 29 234 deaths (35.0%) registered during the observation period.
- an increased risk of death
- time independency in NSAID risk

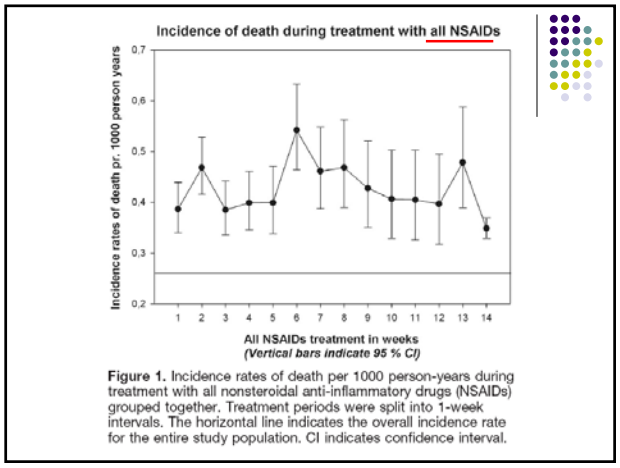
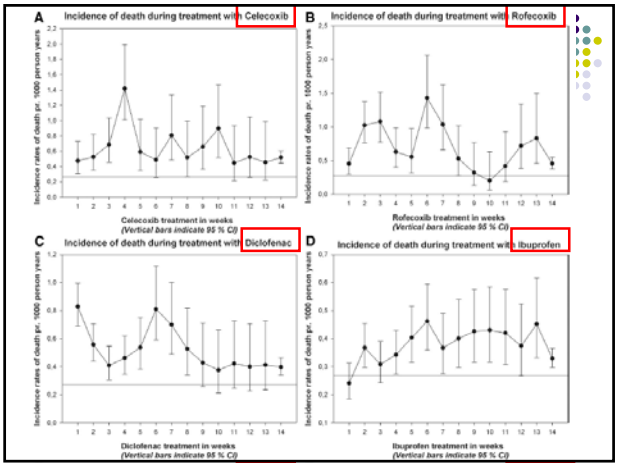
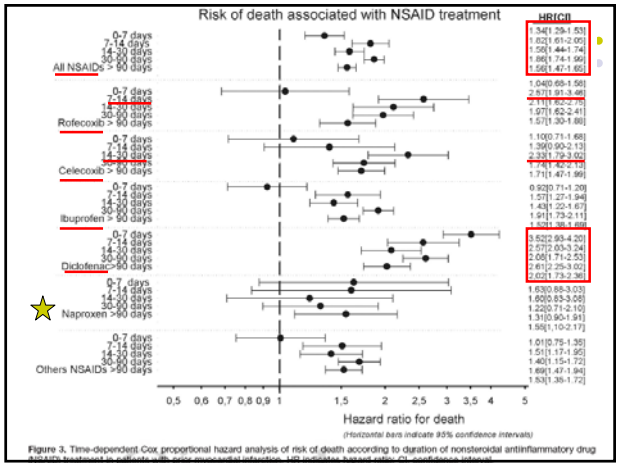


Figure 1. Incidence rates of death per 1000 person-years during treatment with all nonsteroidal anti-inflammatory drugs (NSAIDs) grouped together. Treatment periods were split into 1-week intervals. The horizontal line indicates the overall incidence rate for the entire study population. CI indicates confidence interval.





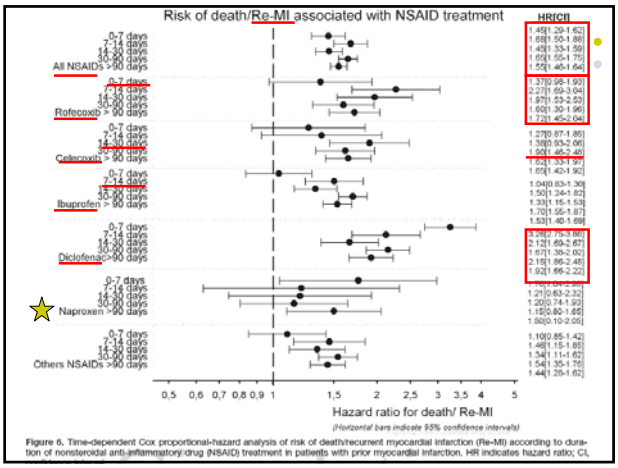


Figure 6. Time-dependent Cox proportional-hazard analysis of risk of death/recurrent myocardial infarction (Re-MI) according to duration of nonsteroidal anti-inflammatory drug (NSAID) treatment in patients with prior myocardial infarction. HR indicates hazard ratio; CI,

Results

- **Supplementary Analysis**
- age and use of diclofenac
  - age-stratified analysis (<60, 60 to 69, 70 to 79, ≧80 years of age)
  - patients ≧80 years of age had a higher risk of death during the first week of treatment (≧ 80 years of age: hazard ratio, 5.49, *P*<0.0001)
- No other relevant interaction was found.

Discussion

- The main results of the study were that the risks of death and death/Re-MI were independent of the duration of NSAID
- The risk with some NSAIDs became apparent immediately (diclofenac) or early (rofecoxib and ibuprofen) after treatment onset.
- These results challenge the view that NSAIDs are not harmful during short-term (1 week) treatment

Discussion

- The VIGOR study: selective COX-2 inhibitor rofecoxib compared with patients taking naproxen
- support previous studies showing that patients with prior MI are at increased risk when taking NSAIDs, especially diclofenac and the selective COX-2 inhibitors.

Discussion

- selective COX-2 inhibitor rofecoxib was increased after only 7 days of treatment (which was withdrawn from the market in 2004)
- the higher risk of death and MI during treatment with diclofenac was increased immediately after the start of treatment, and persisted.

Discussion

- challenge the current recommendations by the AHA
- there essentially appears to be no safe therapeutic window for NSAID treatment
- limit NSAID use in patients with cardiovascular disease and to get the message out to clinicians taking care of these patients that NSAIDs are potentially harmful, even for short-term treatment

Discussion

- naproxen should be the preferred NSAID if NSAID treatment cannot be avoided
- naproxen was associated with higher risk of GII bleeding than rofecoxib, and that GI bleeding in patients with prior MI is associated with worse prognosis.

Study Strengths and Limitations

- The main strength of this study is the completeness of data from a nationwide cohort and the avoidance of selection bias resulting from race, age, sex, socioeconomic status, affiliation to selected hospitals, or healthcare systems.
- The only NSAID available in Denmark over the counter without a prescription is ibuprofen (since 2001) and only in low doses (200 mg) and in limited quantity (100 tablets) at each dispensing.

Study Strengths and Limitations

- The main limitation of the study is inherent to the observational design
- lack of information about important clinical parameters such as blood pressure, body mass index, smoking habits, lipid levels, and left ventricular ejection fraction.
- the patients taking NSAIDs were more prone to be sick than those not treated with these agents

Study Strengths and Limitations

- the first symptoms of coronary heart disease can be interpreted as muscular pain and thereafter progress to MI. NSAID are not recommended or used to treat cardiovascular disease.
- Another limitation is the effect of information bias. The patients do not necessarily take their medications consecutively

Conclusions and Clinical Implications

- This nationwide study of patients with prior MI demonstrated that short-term treatment with most NSAIDs is associated with increased cardiovascular risk.
- commonly used NSAIDs, such as diclofenac, which in some countries is available over the counter without any expert advice on potential sideeffects, were associated with increased risk treatment onset, and the risk continued to persist during the course of treatment

Conclusions and Clinical Implications

- The present results indicate that there is no apparent safe therapeutic window for NSAIDs in patients with prior MI.
- Further studies, preferably randomized clinical studies, are warranted to establish the cardiovascular safety of NSAIDs,

THE END

Thank You