RISK OF HOSPITALISATION FOR MYOCARDIAL INFARCTION AFTER USE OF ROFECOXIB, CELECOXIB AND OTHER NSAID'S

Johnsen SP et al undertook a population-based case-control study to examine the risk of myocardial infarction (MI) among users of various categories of non-Aspirin NSAIDs. They used data from hospital discharge registries and accountees of North Jutlin, Viborg and Aarhus, Denmark and the Danish Civil Registration system. They identified 10,280 cases of first time hospitalisation for MI and 102,797 sex and aged matched non MI population control. All prescriptions for non Aspirin NSAIDs filled before the date of admission for MR were identified using population based prescription data bases. Relative risk estimates for MI were adjusted for a history of cardiovascular disease, hypertension, diabetes mellitus, chronic bronchitis or emphysema, alcoholism, liver cirrhosis, upper gastrointestinal bleeding, rheumatoid arthritis, systemic lupus erythematosis and the use of high dose Aspirin, platelet inhibitors, insulin or oral hypoglycaemic drugs, anti hypertensive drugs, lipid-lowering drugs, oral anti-coagulants, nitrates, Penicillamine, gold, oral glucocorticoids and hormone therapy before the date of admission for MI.

Table 2. Crude and Adjusted Relative Risk Estimates for MI According to Prescription for Celecoxib, Rofecoxib, Other Cox-2 Selective Inhibitors, Naproxen and Other Non-Aspirin NSAIDs.

Category of User	**Cases** (n=9287)	**Controls** (n = 93270)	**Crude RR** (85% Cl)	**Adjusted RR** (95% Cl)
Non user	4178	47122	1.00 (reference)	1.00 (reference)
Rofecoxib				
Current User	119	611	2.23 (1.82 – 2.72)	1.80 (1.47 – 2.21)
New User	39	149	2.97 (2.08 – 4.24)	2.52 (1.74 – 3.64)
Celecoxib				
Current user	71	521	1.56 (1.21 – 2.00)	1.25 (0.97 – 1.62)
New user	35	148	2.87 (1.85 – 3.87)	2.13 (1.45 – 3.13)
Other Cox 2 – selective inhibitor				
Current user	57	398	1.63 (1.24 – 2.16)	1.45 (1.09 – 1.93)
New user	22	68	3.64 (2.25 – 5.90)	3.37 (2.05 – 5.53)
Naproxen				
Current user	26	175	1.68 (1.11 – 2.53)	1.50 (0.99 – 2.29)
New user	4	25	1.82 (0.83 – 5.23)	1.65 (0.57 – 4.83)
Other non-Aspirin NSAID				
Current user	532	3105	1.94 (1.76 – 2.14)	1.68 (1.52 – 1.85)
New user	65	278	2.65 (2.03 – 3.48)	2.65 (2.00 – 3.50)

Individuals were classified as to their most recent use of NSAIDs. Current users were defined as having filled a prescription within 0 to 30 days, new users were defined as having filled their first prescription within 0 – 30 days.

The number of cases of MI in some of the sub groups was small. For example 15 cases of MI occurred in patients taking Celecoxib and 8 cases in patients taking Naproxen in low risk individuals.

This study found elevated risk estimates for MI among current and in particular new users of Rofecoxib and Celecoxib. Elevated risk estimates were also found among current and new users of other Cox 2 selective inhibitors, Naproxen, other conventional non Aspirin NSAIDs or high dose Aspirin. We need to be aware that this study design is always less rigorous than a randomised case control design and confounded by potential misdiagnoses and the well-known association between increased cardiovascular risk factors and osteoarthritis. Individuals with osteoarthritis have a higher risk of vascular events than individuals without osteoarthritis. Patients with rheumatoid arthritis and gout also have a higher risk of vascular disease than individuals without these diagnoses. The authors commented that the elevated risk estimates occurred with all types of NSAIDs and they to some extent reflect the existence of a protopathic bias. This occurs when the indication for being prescribed a drug may be an unrecognised clinical manifestation related to the outcome question. Thus patients who are having angina pectoris may be misdiagnosed as experiencing chest pain of musculoskeletal origin. There is also lack of data on the over the counter sale of NSAIDs. There is also a lack of compliance and duration of actual use data of the prescribed drugs. A non significant increased MI risk has also been noted recently in the TARGET study where Lumiracoxib was compared with Naproxen (relative risk 1.77:85% CI, 0.82 – 3.84), but not Ibuprofen, (relative risk, 0.66:95% CI:0.21 – 2.09). No studies have found an increased risk of MI or other cardiovascular events among users of Celecoxib compared with users of Celecoxib compared with the uses of placebo, uses of other non Aspirin NSAIDs or non users of non aspirin NSAIDs. (references).

This study by Johnsen et al has demonstrated an increased relative risk of myocardial infarction among Celecoxib users and in accordance with the recently halted ATC trial in which a significant increase in the risk of cardiovascular events was found among patients randomised to a daily dose of 400 or 800mg of Celecoxib (reference). The doses of Celecoxib in this trial are high compared with the currently approved dose regimes for osteoarthritis (200mg daily) and rheumatoid arthritis (200 – 400mg daily). No increased cardiovascular risk so far has appeared in two other ongoing trials of Celecoxib, similar in size and duration to the APC trial (reference).