Diclofenac use and cardiovascular risks: series of nationwide cohort studies
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Objective: To examine the cardiovascular risks of diclofenac initiation compared with initiation of other traditional non-steroidal anti-inflammatory drugs, initiation of acetaminophen, and no initiation.

Participants: adults without malignancy; schizophrenia; dementia; or cardiovascular, kidney, liver, or ulcer diseases (that is, with low baseline risk). The study included 1,370,832 diclofenac initiators, 3,878,454 ibuprofen initiators, 291,490 naproxen initiators, 764,781 healthcare seeking acetaminophen initiators, and 1,303,209 healthcare seeking non-initiators. Men accounted for about 45% of diclofenac and ibuprofen initiators, 35% of acetaminophen initiators, and 40% of naproxen initiators. The median age was 46-49 years among NSAID initiators and 56 years among acetaminophen initiators.

Data Source: National Patient Registry covering all Danish hospitals to identify the study population, their comorbidities, and non-fatal endpoints. Each hospital discharge or outpatient visit (since 1977 and 1995, respectively) is recorded in the registry with one primary diagnosis and potentially several secondary diagnoses classified according to the ICD-8 (international classification of diseases, 8th revision) and ICD-10 thereafter. Data on general practice contacts were obtained from the Danish National Health Insurance Service Registry.

The Danish National Prescription Registry was used to identify drug use. Since 1995, this registry has maintained detailed records of all prescriptions dispensed from all Danish pharmacies. Mortality and migration data were obtained from the Danish Civil Registration System, which has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates. Cause of death data were obtained from the Danish Register of Causes of Death.

Design: Eligible individuals were those aged at least 18 years with at least one year of continuous prescription records before date of study entry, who did not meet the exclusion criteria, and who did not redeem NSAID prescriptions in the 12-month period before enrollment.

Non-initiators of NSAIDs and acetaminophen initiators were identified from the general population. Non-initiators were matched to diclofenac initiators by propensity score (based on a logistic regression model including covariates on sex, age, year, comorbidity, and drug treatment use).

Results:

Diclofenac v non-use: Diclofenac initiators had a 50% increased rate of major adverse cardiovascular events compared with non-initiators (incidence rate ratio 1.5, 95% confidence interval 1.4 to 1.7). Event rates consistently increased for all individual outcomes: 1.2-fold for atrial fibrillation or flutter, 1.6-fold for ischemic stroke, 1.7-fold for heart failure, 1.9-fold for myocardial infarction, and 1.7-foldfor cardiac death. Cardiac death was driven by death from heart failure (incidence rate ratio 2.3, 1.3 to 4.2), cardiac arrhythmia (1.9, 1.1 to3.3), and myocardial infarction (1.7, 1.2 to 2.4).

Diclofenac v acetaminophen: Compared with acetaminophen initiators, diclofenac initiators had a 20% increased rate of major adverse cardiovascular events (incidence rate ratio 1.2, 95% confidence interval 1.1 to 1.3), reflecting a 1.2-fold increased rate of ischemic stroke and heart failure and a 1.4-fold increased rate of atrial fibrillation or flutter and myocardial infarction. Although overall there was no association with cardiac death (incidence rate ratio 1.0, confidence interval 0.8 to 1.2), stratification on underlying causes of death revealed a substantial elevated risk of fatal myocardial infarction (incidence rate ratio 1.8, confidence interval 1.2 to 2.6).

Diclofenac v ibuprofen or naproxen: Diclofenac initiators had a 20% increased rate of major adverse cardiovascular events compared with ibuprofen initiators (incidence rate ratio 1.2, 95% confidence interval 1.1 to 1.3) and a 30% increased rate compared with naproxen initiators (incidence rate ratio 1.3, confidence interval 1.1 to 1.5).

With ibuprofen as reference, the incidence rate ratio increased 1.1-fold for atrial fibrillation or flutter and heart failure, 1.2-fold for myocardial infarction, 1.3-fold for ischemic stroke, and 1.5-fold for cardiac death. Cardiac death was driven by death due to heart failure (incidence rate ratio 1.9, confidence interval 1.2 to 3.0), cardiac arrhythmias (incidence rate ratio 1.7, confidence interval 1.1 to 2.7), and myocardial infarction (incidence rate ratio 1.4, confidence interval 1.1 to 1.8).

Compared with naproxen initiators, the incidence rate ratio increased 1.2-fold for ischemic stroke, 1.3-fold for atrial fibrillation or flutter and cardiac death, 1.4-fold for myocardial infarction, and 1.5-fold for heart failure. Consistently, cardiac death was driven by death due to heart failure (incidence rate ratio 1.7, confidence interval 0.6 to 5.0) and myocardial infarction (incident rate ratio 1.5, confidence interval 0.8 to 2.9).

Authors' Conclusion: "Considering its cardiovascular and gastrointestinal risks, however, there is little justification to initiate diclofenac treatment before other traditional NSAIDs."