

Authors and Disclosures

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From Heartwire

NSAID Use Associated With Future Stroke in Healthy Population



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September 8, 2010 (**Stockholm, Sweden**) — Short-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with an increased risk of stroke in a Danish population study including only healthy individuals.

Presenting the study at last week's **European Society of Cardiology (ESC) 2010 Congress**, **Dr Gunnar Gislason** (Gentofte University Hospital, Hellerup, Denmark) said the results could have "massive public-health implications."

"First we found an increased risk of MI with NSAIDs. Now we are finding the same thing for stroke. This is very serious, as these drugs are very widely used, with many available over the counter," Gislason told **heartwire**. "We need to get the message out to healthcare authorities that these drugs need to be regulated more carefully."

Cochair of the session at which the study was presented, **Dr Robert Califf** (Duke Clinical Research Institute, Durham, NC), agreed that the results raised a major public-health issue, especially in the US, where many NSAIDs were available without a prescription.

For the current study, Gislason and colleagues examined the risk of stroke and NSAID use in healthy individuals living in Denmark. He explained to **heartwire** that information on each individual in the Danish population is kept in various national registries. His team started with the whole population of Denmark aged over 10 years. To select just the healthy individuals, they excluded anyone admitted to the hospital within the past five years or those prescribed chronic medications for more than two years. This left a population of around half a million, who were included in the study. By linking to prescribing registries, the researchers found that 45% of these healthy individuals had received at least one prescription for an NSAID between 1997 and 2005. They then used stroke data from further hospitalization and death registries and estimated the risk of fatal and nonfatal stroke associated with the use of NSAIDs by Cox proportional-hazard models and case-crossover analyses.

Results showed that NSAID use was associated with an increased risk of stroke. This increased risk ranged from about 30% with **ibuprofen** and **naproxen** to 86% with **diclofenac**.

Risk of Stroke With Various Nsaids

NSAID	HR (95% CI) for risk of stroke
Ibuprofen	1.28 (1.14–1.44)
Diclofenac	1.86 (1.58–2.19)

Rofecoxib	1.61 (1.14–2.29)
Celecoxib	1.69 (1.11–2.26)
Naproxen	1.35 (1.01–1.79)

Gislason noted that there was also a dose-relationship found, with the increased risk of stroke reaching 90% (HR 1.90) with doses of ibuprofen over 200 mg and 100% (HR 2.0) with diclofenac doses over 100 mg. He pointed out that the results were particularly striking, given that this study was conducted in healthy individuals.

He conceded that his results could have some confounding but noted that the data were controlled for age, gender, and socioeconomic status and the patient population did not include those with chronic diseases. "We also have to think about the degree of confounding needed to nullify risk. It would have to increase risk four- to fivefold, which is very unlikely," he commented.

He said he did not find the results that surprising in view of the accumulating evidence of increased MI risk with these drugs, adding that the mechanism was probably the same. There have been several hypotheses about the mechanism linking NSAIDs with cardiovascular events, including increased thrombotic effect on platelets, the endothelium, and/or atherosclerotic plaques; increasing blood pressure; and effect on the kidneys and salt retention.

Gislason told **heartwire** that there is reluctance among the medical profession to limit the prescribing of these drugs. "The problem is that we don't have randomized trials, and it is very hard to change the habits of doctors. They have been using these drugs for decades without thinking about cardiovascular side effects."

He also stressed that the public needs to be protected by not allowing NSAIDs to be bought without a prescription. He has had some success in this regard in Denmark at least, where diclofenac became available over the counter recently, but after some of the MI data came out, Gislason's group campaigned the health authorities, and it has now become a prescription-only drug again. But he noted that many more NSAIDs are available over the counter in the US.

He believes the harmful effects of these agents are relevant to huge numbers of people. "If half the population takes these drugs, even on an occasional basis, then this could be responsible for a 50% to 100% increase in stroke risk. It is an enormous effect."

These results have been partly published in *Circulation: Cardiovascular Quality and Outcomes* earlier this year [1]. Gislason told **heart wire** that the novelty of the results presented at the ESC meeting was that "we had further analyzed our data regarding specific stroke and looked at the risk of ischemic stroke, and we confirmed that the risk of ischemic stroke was substantially elevated." He added: "We are in the process of analyzing these data related to time to risk and the effect of duration of treatment on stroke risk."

References

1. Fosbøl EL, Folke F, Jacobsen S, et al. Cause-specific CV risk associated with NSAIDs among healthy individuals. *Circ Cardiovasc Qual Outcomes* 2010; 3:395-405. [Abstract](#)