

## Warfarin increases risk of stroke among atrial fibrillation patients in first 30 days of use

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Patients with atrial fibrillation – an irregular and often abnormally fast heartbeat – have nearly double the risk of suffering a stroke in the first 30 days after starting to take the anti-clotting drug warfarin compared to non-users, according to a study of over 70,000 patients.

The study, published online today (Thursday) in the *European Heart Journal*, found that the risk was particularly high in the first week after patients started to take the drug. In contrast, once the first 30 days had elapsed, the risk of a <u>stroke</u> was halved in patients taking <u>warfarin</u> compared to non-users.

Atrial fibrillation increases the risk of patients suffering a stroke, and warfarin is frequently prescribed for these patients to reduce the likelihood of this happening. However, randomised controlled trials of other anti-clotting drugs have suggested that there might be an increased risk of a stroke at the point when patients move from the trial drugs to warfarin. In addition, it has already been established that there is a possibility that warfarin leads temporarily to a hypercoagulable state – one in which the blood becomes more sticky and more likely to develop dangerous blood clots in the veins or arteries. This is thought to be due to the different effects of warfarin on the production of certain blood clotting factors that are dependent on Vitamin K.

Dr Laurent Azoulay, Assistant Professor in the Department of Oncology



at McGill University (Montreal, Canada) and Project Leader at the Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital in Montreal, led the research. "There is no question that warfarin is highly effective in preventing strokes in patients with atrial fibrillation. Thus, our finding that the initiation of warfarin may be associated with an increased risk of stroke should not deter physicians and patients from using this drug, since this likely affects a small number of patients. Future studies should confirm our results, and identify the small subset of patients who may be at risk. However, the results of our study suggest that physicians should be vigilant when initiating warfarin, particularly in the first week of use," he said.

"An interesting finding was that patients with a history of stroke prior to their atrial fibrillation diagnosis were at higher increased risk of developing a stroke during the initiation of warfarin. This is consistent with the hypothesis that the risk may be highest in patients with hypercoagulable states, which provides insight on the possible biological mechanisms that may be at play in this association.

"To our knowledge, this is the first population-based study to investigate whether the initiation of warfarin is associated with an increased risk of ischaemic stroke – a stroke caused by a blockage in an artery leading to the brain."

The researchers analysed data from 70,766 patients aged 18 or over, who were diagnosed with <u>atrial fibrillation</u> between 1 January 1993 and 31 December 2008. The study was carried out using the UK Clinical Practice Research Datalink, the world's largest primary care database. The researchers followed the patients for up to 16 years until an ischaemic stroke, death, end of registration with their primary care practice or end of the study period, whichever came first.

During that time, a total of 5519 patients experienced a stroke (two



percent per year). During the first 30 days after starting warfarin, there was a 71% (nearly double) increased risk of ischaemic stroke when compared with patients taking no anti-coagulant drugs. The highest risk was in the first week of use, peaking on the third day after starting warfarin when there was a 133% (2.3-fold) increased risk of stroke. After 30 days, the risk of stroke among the warfarin patients halved. If the patients had a history of previous ischaemic stroke, they had a 245% (2.5-fold) increased risk during the first 30 days.

The researchers believe that the reason for the difference in the effects of warfarin may be that while the drug blocks the activation of clotting factors II, VII, IX and X, it also deactivates two other proteins, C and S, which are anticoagulants. Rapid depletion of protein C, in particular, might lead to a temporary hypercoagulable state.

The senior author of the study, Professor Samy Suissa, James McGill Professor of Epidemiology, Biostatistics and Medicine at McGill University (Montreal, Canada), said: "While these findings need to be confirmed in other settings, it would be imperative to also investigate whether the newer popular anticoagulants also carry this early risk." In the meantime, he suggests that "a bridging strategy using heparin – an injectable anticoagulant – at the initiation of warfarin treatment could be considered as a way to reduce the increased risk observed in the first 30 days of use."

The researchers hope to repeat the study using databases from other countries and settings.

**More information:** "Initiation of warfarin in patients with atrial fibrillation: early effects on ischaemic strokes", by Laurent Azoulay, Sophie Dell'Anielllo, Teresa A. Simon, Christel Renoux, and Samy Suissa. *European Heart Journal*. <u>DOI: 10.1093/eurheartj/eht499</u>



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