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Clinical Research

Does Digoxin Increase the Risk of Ischemic Stroke and Mortality in Atrial Fibrillation? A Nationwide Population-Based Cohort Study

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ABSTRACT

Background: Digoxin and related cardiac glycosides have been used for almost 100 years in atrial fibrillation (AF). However, 2 recent analyses of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial showed inconsistent results regarding the risk of mortality associated with digoxin use. The goal of the present study was to investigate the relationship between digoxin and the risk of ischemic stroke and mortality in Asians.

Methods: This study used the National Health Insurance Research Database (NHIRD) in Taiwan. A total of 4781 patients with AF who did not receive any antithrombotic therapy were selected as the study

RÉSUMÉ

Introduction : La digoxine et les glucosides cardiotoniques associés ont été utilisés depuis presque 100 ans contre la fibrillation auriculaire (FA). Cependant, 2 analyses récentes de l'essai AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) ont montré des résultats contradictoires concernant le risque de mortalité associé à l'utilisation de la digoxine. Le but de la présente étude était d'examiner le lien entre la digoxine et le risque d'accident vasculaire cérébral (AVC) ischémique et de mortalité chez les Asiatiques.

Méthodes : Cette étude a utilisé la banque de données NHIRD (National Health Insurance Research Database de Taïwan). Un total de

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its incidence is projected to rise continuously over the next few decades.[1,2] Although the technique of catheter ablation for AF has greatly advanced in recent years, stroke prevention with anticoagulation therapy and long-term rate control remain central to the management of AF. Digoxin and related cardiac glycosides have been used for more than 200 years for treatment of heart failure and for almost 100 years for rate control in AF.[3] The European Society of Cardiology guideline for the management of AF recommends digoxin as 1 of the choices for long-term rate control in patients with AF.[4] The focused 2012 update of the Canadian Cardiovascular Society AF guideline recommends digoxin use in addition to β-blockers for controlling ventricular rate in patients with heart failure.[5] However, in the post hoc analysis of the Atrial Fibrillation Follow-up

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population. Among the study population, 829 participants (17.3%) received the digoxin treatment. The risk of ischemic stroke and mortality in patients who received digoxin and those who did not was compared.

Results: The use of digoxin was associated with an increased risk of clinical events, with an adjusted hazard ratio of 1.41 (95% confidence interval [CI], 1.17-1.70) for ischemic stroke and 1.21 (95% CI, 1.01-1.44) for all-cause mortality. In the subgroup analysis based on coexistence with heart failure or not, digoxin was a risk factor for adverse events in patients without heart failure but not in those with heart failure (interaction $P < 0.001$ for either end point). Among patients with AF without heart failure, the use of β-blockers was associated with better survival, with an adjusted hazard ratio of 0.48 (95% CI, 0.34-0.68).

Conclusions: Digoxin should be avoided for patients with AF without heart failure because it was associated with an increased risk of clinical events. β-Blockers may be a better choice for controlling ventricular rate in these patients.

4781 patients souffrant de FA qui ne recevaient aucun traitement antithrombotique ont été sélectionnés en tant que population à l'étude. Parmi la population à l'étude, 829 participants (17,3 %) ont reçu le traitement par la digoxine. Le risque d'AVC ischémique et de mortalité des patients qui recevaient la digoxine et de ceux qui ne la recevaient pas a été comparé.

Résultats : L'utilisation de la digoxine a été associée à une augmentation du risque d'événements cliniques selon le rapport de risque ajusté de 1,41 (intervalle de confiance [IC] à 95 %, 1,17-1,70) pour l'AVC ischémique et de 1,21 (IC à 95 %, 1,01-1,44) pour la mortalité toutes causes confondues. Dans l'analyse en sous-groupes en fonction de la coexistence de l'insuffisance cardiaque ou non, la digoxine a été un facteur de risque d'événements indésirables chez les patients ne souffrant pas d'insuffisance cardiaque, mais non chez ceux souffrant d'insuffisance cardiaque (interaction $P < 0{,}001$ pour l'un ou l'autre des critères de jugement). Parmi les patients souffrant de FA sans insuffisance cardiaque, l'utilisation de β-bloquants a été associée à une meilleure survie selon un rapport de risque ajusté de 0,48 (IC à 95 %, 0,34-0,68).

Conclusions : La digoxine devrait être évitée chez les patients souffrant de FA sans insuffisance cardiaque puisqu'elle a été associée à une augmentation du risque d'événements cliniques. Les β-bloquants peuvent être un meilleur choix pour maîtriser la fréquence ventriculaire de ces patients.

Investigation of Rhythm Management (AFFIRM) trial performed by Whitbeck et al.,[6] digoxin use was associated with a 41% increased risk of all-cause mortality, a 35% increased risk of cardiovascular mortality, and a 61% increased risk of arrhythmic mortality. Interestingly, using the same data set, a recent study showed a completely different conclusion regarding the safety of digoxin in the treatment of AF, demonstrating that digoxin was not associated with increased mortality using propensity-matched analysis.[7] Therefore, whether the use of digoxin is safe in patients with AF remains uncertain, and it would be interesting to investigate this issue in a population-based study. In addition, digoxin use has been reported to increase platelet activity, which could predispose patients to thrombosis and vascular events.[8] However, whether the use of digoxin is associated with an increased risk of ischemic stroke has not been fully explored. The goal of the present study was to investigate the association of the use of digoxin and the risk of ischemic stroke and mortality in patients with AF.

Methods

Database

This study used the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes. The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. The NHIRD was a cohort data set that contained all the medical claims data for 1 million beneficiaries who were randomly sampled from the 25.68 million enrollees under the NHI program. These random samples have been confirmed by the Taiwan National Health Research Institutes to be representative of the Taiwanese population.[9] In this cohort data set, the patients' original identification numbers were encrypted to protect their privacy, but the encrypting procedure was consistent so that a linkage of the claims belonging to the same patient was feasible within the NHI database and could be followed continuously. The database, with a large sample size, provided a good opportunity to study the risk of ischemic stroke and mortality in patients with AF who receive digoxin and those who do not.

Study population

From January 1, 2000 to December 31, 2009, a total of 4781 patients aged $\geq$ 18 years with newly diagnosed AF who did not receive any antithrombotic therapy, including antiplatelet agents and oral anticoagulants, were identified from the NHIRD. The reasons that we excluded patients who received antithrombotic drugs included the following: (1) Underuse of warfarin was a common problem in daily practice when managing patients with AF, especially in Taiwan,[10,11] and exclusion of these patients may therefore minimize the selection bias. (2) The detailed data regarding the international normalized ratio and time in therapeutic range for warfarin users were not recorded in NHIRD, and the lack of these parameters may significantly confound the analysis regarding the risk of ischemic stroke. The CHA_2DS_2-VASc (Congestive Heart Failure, Hypertension, Age $\geq$ 75, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack, Vascular Disease, Age 65 to 74, Female Gender) score was calculated for each patient based on a point system in which 2 points are assigned for a history of stroke or transient ischemic attack or an age $\geq$ 75 years, and 1 point is assigned for each of the following factors: age 65-74 years and a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque, or peripheral artery disease),