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Atrial fibrillation, liver disease, antithrombotics and risk of cerebrovascular events: A population-based cohort study

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ABSTRACT

Background: Whether patients with atrial fibrillation (AF) and liver disease are also prone to cerebrovascular events and respond similarly favorably to antithrombotic therapy remains under-investigated.
Methods: Patients ≥18 years with newly-diagnosed AF in the period 2005 to 2009 were scrutinized from the "Longitudinal Health Insurance Database 2005" (1 million beneficiaries) of Taiwan's National Health Insurance Institute. Patients were categorized into the Liver ($N = 433$) or the Non-liver ($N = 3490$) cohort according to whether they had a diagnosis of advanced liver disease. Patients were then followed to determine cumulative incidence of hospitalization-requiring cerebrovascular events, preventive effects of antithrombotics, and predictors of cerebrovascular events by Cox regression analysis.
Results: Within a mean follow-up of 3.3 ± 1.4 years, ischemic stroke (89.2 vs. 50.3 per 1000 person-years, adjusted HR 1.502, 95% CI 1.207–1.868, $p < 0.001$) and overall cerebrovascular events (102.3 vs. 56.4 per 1000 person-years, adjusted HR 1.535, 95% CI 1.251–1.883, $p < 0.001$) occurred significantly more often in the Liver than in the Non-liver cohort. Cox models identified aging (≥65 years), DM, and CHA2DS-VASc score ≥ 2 points as risk factors for overall cerebrovascular events in the Liver cohort, whereas antiplatelet agents (HR 0.932, 95% CI 0.128–6.803, p = NS) and vit-K antagonistic anticoagulants (HR 1.087, 95% CI 0.150–7.862, p = NS) showed no correlation.
Conclusion: AF patients comorbid with advanced liver disease are more vulnerable to ischemic and therein overall cerebrovascular events, especially in those with old age, DM, or high CHA2DS-VASc scores. This propensity to cerebrovascular events, however, can't be altered by antithrombotic therapy.

1. Introduction

Atrial fibrillation (AF) is the most common adult arrhythmic disease [1] that can provoke thromboembolism to the systemic vasculature and cause serious ischemic events in multiple organs [2–4]. Cerebrovascular system is a susceptible target of AF-related embolic effects that often lead to catastrophic neurological consequences including disabling morbidities and mortality [2,5]. Anti-thrombotic agents have thus been recommended as an essential therapy for such patients to prevent ischemic cerebral events especially for those stratified by the CHA2DS2-VAS2 scoring system as having a higher embolic risk [6]. However, use of these agents could potentially cause serious hemorrhagic side effects in some patient population with bleeding vulnerability and thus requires precedent identification of such subjects to avoid occurrence of these potentially disastrous complications [6,7].

The liver is a crucial organ for production of proteins with diverse functions. Advanced liver disease can impede the synthesis of most proteins, including both pro-coagulation and anti-coagulation factors, and lead to either a bleeding [8,9] or a thrombotic tendency [10]. Thus, whether AF patients with advanced liver disease still have a higher hazard of ischemic cerebral stroke or in contrast are exposed to an elevated risk of cerebral hemorrhage remains controversial [11–13], rendering the decision to apply anti-coagulant therapy to these patients a challenging clinical dilemma [14,15]. To clarify this issue, this study attempted to determine if patients with AF and advanced liver disease are also at risk of thromboembolism, and whether antithrombotics should similarly be given to these patients to improve overall

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cerebrovascular outcome. The research was conducted by examining a large-scale database maintained by Taiwan's National Health Insurance (NHI) program [16] to recruit and follow up patients with new-onset AF for future cerebrovascular events. Data on the incidence of hospitalization-requiring ischemic stroke, systemic embolism, and cerebral hemorrhage in AF patients with or without hospitalization-requiring liver disease were collected from the database. The results of this study may shed light on the impact of advanced liver disease on the cerebrovascular outcome of patients with AF, and may provide a guide for the optimal use of antithrombotics for AF patients comorbid with liver disease to improve their cerebrovascular prognosis.

2. Methods

2.1. Research database

The NHI program in Taiwan was instituted in March 1995 and currently provides all forms of health care services for about 99% of the nation's 23.74 million residents [3,4,16]. All facilities offering medical services are legally required to submit reimbursement claims for medical fees as well as treatment data every month to the NHI Administration. These claims records are stored by Taiwan's National Health Research Institutes (NHRI) in the National Health Insurance Research Database (NHIRD) which makes data available to scientists for research purposes [3–5]. The present study collected data from the Longitudinal Health Insurance Database 2005 (LHID 2005), which contains the original claims data of 1 million patients randomly sampled from the 2005 Registry Beneficiaries in the NHIRD. This random sampling of patients in the LHID 2005 has been confirmed by the NHRI to be representative of the general Taiwanese population, and has no statistically significant differences in age or gender compared with all other patients in the NHIRD. All of these patients' inpatient and outpatient claims records, if any, from 1998 to 2010 were collected and analyzed. Patients' information and characteristics are stored in the database, as well as detailed information about prescriptions, including the names of drugs, prescribed dosage, and drug use duration. The diagnoses reported in NHI claims are recorded using the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and received a priori approval by the institution's human research committee. The requirement to obtain informed consent from each patient was waived by the Institutional Review Board of Taichung Veterans General Hospital.

2.2. Patients

Among the one million subjects included in the LHID 2005, those who were older than 18 years and had ever utilized any medical service between 2005 and 2009 were further analyzed. Patients with newly diagnosed AF (ICD-9-CM 427.31 recorded as at least one inpatient or three consecutive outpatient diagnoses between 2005 and 2009, but not from 1997 to 2004) were included in the study. These enrolled patients were then assigned to the "Liver Cohort" if they had ever been diagnosed with and hospitalized for any of the advanced liver diseases (hepatocellular carcinoma, ICD-9-CM 155.0; liver cirrhosis, ICD-9-CM 571; other chronic hepatic diseases, ICD-9-CM 570, 572, 573; hepatitis A/B/C/D, ICD-9-CM 070.0–070.9) at or before the diagnosis of AF, or were assigned to the "Non-liver Cohort" if they didn't have any of the aforementioned advanced liver diseases. The time at which the diagnosis of AF was first made was designated as the index date. The study endpoint was defined as the first hospitalization-requiring cerebrovascular event, including ischemic cerebral stroke (ICD-9-CM 433–438), systemic thrombosis/embolism (ICD-9-CM 444, viewed as ischemic stroke-equivalent), and non-traumatic intracranial hemorrhage (ICD-9-CM 430–432). The follow-up period was from the index date to the date of the first cerebrovascular event, withdrawal from NHI, death during any subsequent inpatient course, or until the end of 2010, depending on which occurred first.

2.3. Antithrombotics

Use of contemporarily available oral antithrombotic drugs, including antiplatelet agents (aspirin, ticlopidine, dipyridamole, clopidogrel) and vitamin-K antagonists (VKA, i.e., warfarin) for AF stroke prevention or for other comorbid diseases was retrieved from outpatient and inpatient claims data of all enrolled patients in the LHID 2005. Those ever prescribed with antiplatelet agents at the occurrence of any cerebrovascular events were regarded as users of antiplatelet agents. Adherence to VKA was quantitatively categorized by proportion of days covered (PDC) by this agent, as described elsewhere [3,4].

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Normally distributed continuous data of AF patients comorbid with advanced liver disease (Liver Cohort) and those without it (Non-liver Cohort) were compared by unpaired Student's *t* test, while nonparametric continuous data were compared by Mann–Whitney *U* test. Kaplan–Meier survival curves for cerebral hemorrhage, ischemic stroke, peripheral arterial embolism (considered to be equivalent to ischemic stroke) and overall cerebrovascular events were respectively constructed for the two patient cohorts and

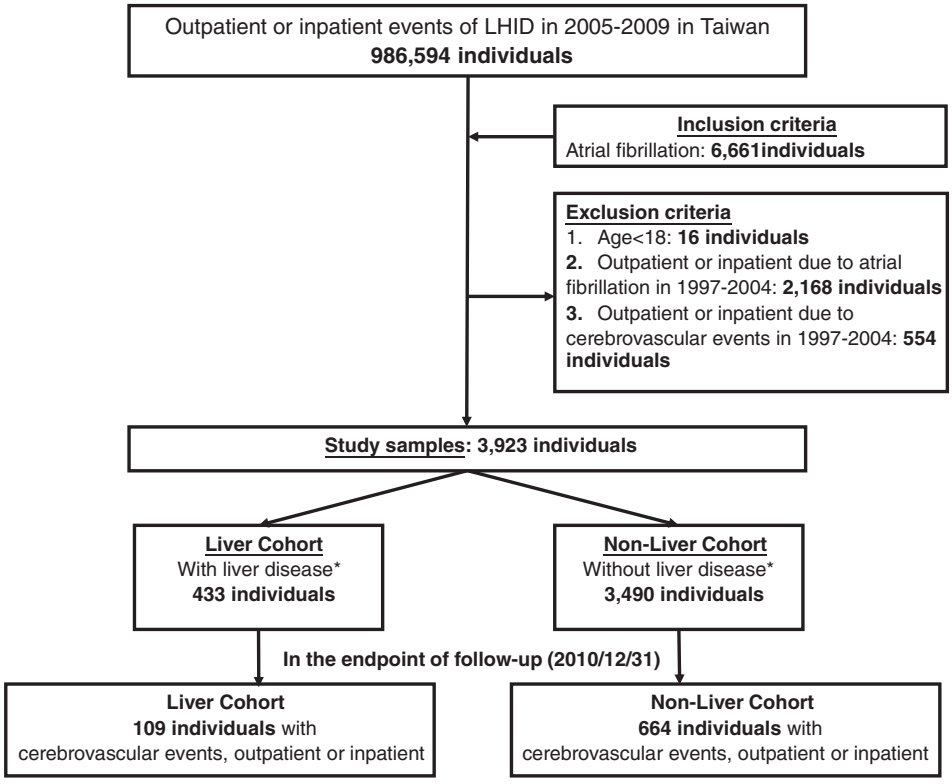

Fig. 1. Algorithm of the study. LHID = Longitudinal Health Insurance Database; Atrial fibrillation: ICD-9-CM 427.31; Cerebrovascular events: ICD-9-CM 430–438, 444; Liver disease: including hepatoma (ICD-9-CM 155.0), chronic liver disease/liver cirrhosis/other hepatic diseases (ICD-9-CM 570–573), and hepatitis A/B/C/D (ICD-9-CM 070.0–070.9).