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Thrombosis prevention in atrial fibrillation with concomitant cirrhosis: oral anticoagulation may not be worth the risks

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ABSTRACT   A critical appraisal and clinical application of Kuo L, Chao T, Liu C, et al. Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention? *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*. 2017;6(6):e005307. doi: 10.1161/JAHA.116.005307.

Keywords: oral anticoagulation, atrial fibrillation, cirrhosis

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Clinical Context

Lisa Davis (pseudonym), a 55-year-old Caucasian woman with a long history of nonalcoholic steatohepatitis eventually progressing to cirrhosis was admitted to the hospital for decompensation of her cirrhosis including ascites and hepatic encephalopathy. She was treated with return of her mental status and resolution of her ascites. The patient and family were working to cope with her prognosis, and despite a solid support system, the prospect of liver transplant weighed on them all. While in the hospital, Ms. Davis admitted to feeling episodes of palpitations previously attributed to anxiety about her condition, and it was discovered that the patient was having episodes of atrial fibrillation (AF). To avoid thrombotic complications including ischemic stroke, anticoagulation is beneficial to patients with AF.[1] Ms. Davis and team wondered what the long-term management of her concomitant diseases would entail. The patient had a family history of stroke in her mother and was concerned about her personal stroke risk, compounded by the effect cirrhosis has on coagulation. Her CHA2DS2-VASc score was 3 (female, history of hypertension and diabetes) classified as "moderate-high" risk for stroke. The decision to initiate Ms. Davis on anticoagulation, however, would be complicated by the coagulation derangements that occur in cirrhosis, which include both increased bleeding and thrombotic risk.[2]

Clinical Question

Is oral anticoagulation for stroke prevention in atrial fibrillation worth the bleeding risk in patients with cirrhosis?

Research Article

Kuo L, Chao TF, Liu CJ, et al. Liver cirrhosis in patients with atrial fibrillation: Would oral anticoagulation have a net clinical benefit for stroke prevention? *J Am Heart Assoc*. 2017;6(6):e005307. doi: 10.1161/jaha.116.005307

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Related Literature

A search of PubMed was performed using the terms "atrial fibrillation", "cirrhosis" or "cirrhotic", and "anticoagulation" in the title or abstract returned 53 results, and the titles and abstracts of these results were analyzed for papers relevant to this topic. This yielded 11 results that were analyzed to determine relevance and ability to answer the clinical question. None of the results available were randomized controlled trials.

Two publications on anticoagulation in cirrhosis in the context of portal or splanchnic vein thrombosis were determined to be relevant, however given the clinical scenario pertains to atrial fibrillation these were excluded.[3,4] A review from a symposium on Intensive Care and Emergency Medicine from Belgium referred to all our search terms only separately, and thus was omitted.

One study addressed anticoagulation as a risk for traffic accidents, and cirrhosis was found to be an additional risk factor for traffic injury.[5] Another was a case report describing a patient with relative hypersplenism from cirrhosis, who was newly diagnosed with atrial fibrillation.[6] While potentially of interest to patient care, none aid in answering the clinical question.

Three papers discussed using Warfarin versus direct oral anticoagulant (DOAC) medications in patients with cirrhosis.[7-9] The Intagliata paper was an abstract addressing the topic in general terms.[7] The Hum paper was a retrospective cohort study of patients with cirrhosis who were prescribed either a DOAC or Warfarin, comparing major bleeding episodes as well as recurrent thrombus or stroke between the two groups.[8] 27 patients with cirrhosis were prescribed a DOAC and 18 were prescribed a Vitamin K antagonist (such as Warfarin) or low molecular weight heparin, and DOACs were found to have less major bleeding risk while maintaining efficacy. The small sample size of 27 patients also contributed to the inferiority of the Hum paper. The Goriacko paper was a retrospective cohort study, analyzing 75 patients on DOACs and 158 on Warfarin with chronic liver disease and AF, finding no significant difference in all-cause bleeding rates.[9] Though these three papers may address a relevant follow-up to our question, their primary aim was to address bleeding risk of specific anticoagulants and were therefore inferior for our study of stroke prevention.

The Choi paper and Kuo et al. paper both evaluated patients with liver cirrhosis and atrial fibrillation on Warfarin vs no anticoagulation. Both analyzing data of patients with AF and cirrhosis, the Choi paper had a total of 465 patients and did not separate participants based on CHA2DS2-VASc score, used to calculate stroke risk in AF patients, leaving the study vulnerable to error based on differences in pre-existing risk.[10,11]

The Kuo et al. paper had 9056 with liver cirrhosis, AF, and a CHA2DS2-VASc score ≥ 2.[12] This paper assessed net clinical benefit between no treatment, antiplatelet therapy, and anticoagulation therapy. Using hazard ratios based on ischemic stroke and intracranial hemorrhage (ICH) events, net clinical benefit was assessed using a large study population stratified based on risk factors and risk scores. For all these reasons, the Kuo et al. paper is most likely to guide clinical decision making and was therefore chosen for analysis.

Critical Appraisal

This publication describes a retrospective cohort study with a CEBM evidence level of 2b. The primary outcome was the occurrence of ischemic stroke with confirmatory brain imaging, including CT or MRI. The study used the National Health Insurance Research Database (NHIRD) of the Taiwan universal health insurance program for all Taiwanese residents, over 23 million. In patients older than 20 years old with liver cirrhosis, AF, and a CHA$_2$DS$_2$-VASc score ≥ 2, 5,532 patients (61.1% of study population) received no anti-platelet or anti-coagulation, 2,770 patients (30.6%) received anti-platelet agents, and 754 (8.3%) received warfarin. AF diagnosis was used if it was a hospital discharge diagnosis or confirmed at least twice in an outpatient setting.

Analysis of net clinical benefit (NCB) was done using the formula: (Ischemic stroke rate no treatment−Ischemic stroke rate anti−thrombotic therapies) −weighting factor× (ICH rate anti−thrombotic therapies−ICH rate no treatment). The weighting factor reflects the relative impact of an ICH while on warfarin or anti-platelet treatment versus ischemic stroke on no treatment. A positive NCB would favor treatment (warfarin) over no treatment. Ischemic stroke and ICH incidence were calculated by dividing the number of events by person-time at risk, and risk was assessed using Cox regression analysis. The design was strengthened by adjustment of analysis for variables, including age, sex, CHA$_2$DS$_2$-VASc, COPD, hyperlipidemia, malignancy, autoimmune diseases, end stage renal

disease, hepatitis B and C infection, hepatic encephalopathy, esophageal varices with bleeding, degree of urbanization, and income level.

Table 1 in Kuo et al. delineates the baseline characteristics of patients who received different therapies. In separating patients between "No Antithrombotic Therapy" (n=5532), "Antiplatelet Agents" (n=2770), and "Warfarin" (n=754) there were some baseline differences in characteristics between those who received different therapies. Of those who received no antithrombotic therapy, 39.7% had a previous stroke/TIA versus 45.9% for both antiplatelet agents and Warfarin. It is worth noting that those who received no antithrombotic therapy had less history of stroke and TIA as well as previous vascular disease. Our patient was a 55-year-old female, and thus was significantly younger than the baseline population in the study with an average age of 73.1 ± 11.2 years. Her CHA2DS2-VASc score was 3, on the lower end of the range of 4.7 ± 1.8 in the study population.

The analysis found that compared to no antithrombotic therapy, antiplatelet therapy had a similar risk of ischemic stroke (HR=1.00, 95%CI=0.85-1.18, P=0.970), but risk was significantly lowered among warfarin users (HR=0.71, 95%CI=0.51-0.99, P=0.047). There were no significant differences found in ICH rates between untreated patients and those taking antiplatelets or warfarin. They concluded that anticoagulation should be considered for AF patients with liver cirrhosis, given a positive NCB compared to being left untreated or using antiplatelet therapy. Their results demonstrated a NNT of 84 and NNH 75.2.

The authors used NCB as the measure of whether treatment is overall favorable. NCB has become an objective measure used to weigh risks and benefits and determine the overall impact of therapy. Though the formula used to generate NCB was calculated using weights from established studies and presented them separately (Table 3 in Kuo et al.), it requires use of a weighting factor to reflect the impact of ICH versus an ischemic stroke, a factor which has not been standardized. Judging life-threatening bleeding risk based only on this mathematical computation may not be representative of the impact, and additional metrics that measure the burden of disease, such as disability-adjusted-life-years (DALY) could also be considered. Additionally, the NCB was calculated solely looking at ICH to evaluate bleeding risk, which may not be sufficient to evaluate bleeding risk in all patients. Significant morbidity and mortality can occur from non-ICH bleeding, such as severe gastrointestinal bleeding or internal hematoma, and these risks need to be taken into consideration as well.

A threshold of CHA_2DS_2-VASc score ≥ 2 was used to qualify patients for this study. This equates to a 2.2% risk of ischemic stroke per year.[13] This was deemed to be an appropriate cutoff, as using a lower CHA_2DS_2-VASc score of 1 equates to only a stroke risk of 0.6% per year. Though a score of 3 is equate to a risk of 3.2% of ischemic stroke per year, 2 seems to be an appropriate cutoff given the fact that their baseline characteristics (Table 1 in Kuo et al.) indicate the average of CHA_2DS_2-VASc score of patients was 4.7 ± 1.8.

The patients were not recruited, but the access to almost the entirety of the Taiwanese population database minimizes the amount of participation bias. While this also attempts to minimize selection bias, the sample is only from Taiwan which leaves the study unclear on its generalization to other populations. With a cohort study, the treatments were not randomized, and the study does not address treatment criteria, leaving it vulnerable for indication bias. Indication bias (also referred to as confounding by indication) occurs when the risk of an adverse event is related to the indication for treatment, but not the use of the treatment itself. This cohort study is vulnerable to lessened validity due to differences in selection of treatment either by patients or providers depending on the indication for no-treatment, antiplatelet, or Warfarin therapy at the time of that decision. The data was not available for Child-Pugh or MELD scores, used to account for liver disease severity, and the inability to quantifiably stratify patients based on disease severity other than variceal bleeding and hepatic encephalopathy makes the article less clinically applicable.[14]

Clinical Application

Our patient with cirrhosis and AF had concerns about her risk of stroke given her coagulation derangements. The Kuo et al. paper concluded that Warfarin had a net clinical benefit when taking the risks of ischemic stroke versus ICH into account. When Ms. Davis came to us, she had developed advanced decompensated cirrhosis, and thus this paper may not be applicable to her since it did not account for disease severity or Child-Pugh scores. Ms. Davis was not Taiwanese and being limited to one nationality makes it difficult to generalize to our patient. The thoughtful design of the Kuo et al. paper is outweighed by its weaknesses and lack of RCT evidence, resulting in an inability to sufficiently answer our clinical question.

As medicine continues to advance in our abilities to take care of patients with advanced liver disease, we must learn to concurrently manage other serious medical conditions. While Ms. Davis was fearful of her stroke risk due to a family history, she understood the compounding factor her cirrhosis played, and the concern that her cirrhosis would lead to higher risk of bleeding if anticoagulation was added. Ultimately, after much discussion between our patient and her team, a shared decision was made not to use anticoagulation at that time. Although still fearful of her increased risk due to her underlying disease, Ms. Davis was optimistic for a liver transplant and hoped that post-transplant she could do more about lowering her stroke risk.

Based on the evidence presented in the Kuo et al. paper, there is not enough support to conclude the benefit of anticoagulation in patients with cirrhosis and atrial fibrillation outweighs the risks. As physicians, we have studied evidence and understand that there is risk of harm and risk of benefit associated with treatments that must be weighed. Our patients are not always as aware of this tradeoff, and it is our duty to involve their values in the decision-making process.

Learning points:

1. Patients with atrial fibrillation are at an increased risk of stroke, and the coagulation derangements that occur with cirrhosis complicate this problem further.

2. Warfarin has been used to minimize risk of ischemic stroke in patients with AF and cirrhosis, although evidence from RCTs is not available to support nor refute this. When making clinical decisions in this regard, patient goals and characteristics must be taken into consideration.

3. In critically appraising research for treatment, the type of study must be considered, as cohort studies may not employ effective randomization to evaluate the true strengths of a treatment. The population must also be noted, as the evidence in this Taiwanese population suggested anticoagulation should be used for patients with AF and liver cirrhosis, but further study in the US is needed to reflect our population.

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