Anticoagulation for Atrial Fibrillation in Cirrhosis of the Liver: Are Low-Dose Non-Vitamin K Oral Anticoagulants a Reasonable Alternative to Warfarin?

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Atrial fibrillation (AF) is a growing global epidemic associated with significant morbidity and mortality.[1,2] One of the most devastating complications associated with AF is stroke, a highly preventable event through the appropriate use of oral anticoagulation therapy. Furthermore, strokes associated with AF have an increased likelihood of causing death or disability.[3] Although oral anticoagulation therapy can significantly reduce the risk of AF-related stroke, numerous international registries have demonstrated that guideline-recommended prescription of anticoagulation remains suboptimal.[4] A major advance in stroke prevention in recent years has been the emergence of non-vitamin K oral anticoagulants (NOACs) given their superior efficacy and safety, predictable effect without routine monitoring, and fewer interactions compared with warfarin. The availability of NOACs is likely to be of great benefit in improving the rate of appropriate anticoagulation use and thus stroke prevention. However, despite increasing familiarity and comfort with their general use, there are still specific clinical situations in which more data are required to increase physician confidence in their efficacy and safety.

It is in this context that in the current issue of the *Journal of the American Heart Association* (*JAHA*) Dr Lee and colleagues examine the use of anticoagulation for AF in a large cohort with 2 important characteristics: Asian ethnicity and comorbid cirrhosis.[5] Using the Taiwan National Health Insurance Database, individuals with AF and cirrhosis were identified with *International Classification of Diseases*, *Ninth Revision* and *Tenth Revision* (*ICD-9* and *ICD-10*) coding. An analysis was undertaken to compare outcomes of cirrhotic individuals with AF treated with NOACs (dabigatran, apixaban, or rivaroxaban) compared with warfarin. A total of 1438 individuals were prescribed NOAC therapy and 990 were prescribed warfarin. The major outcomes examined in this study were ischemic stroke or systemic embolism, intracranial hemorrhage, major gastrointestinal bleeding, and major bleeding, as identified similarly by *ICD* codes. Propensity score–based stabilized weights were utilized to balance covariates in these analyses. Over a mean follow-up period of just over 1 year, the authors report that treatment with NOAC therapy was associated with a similar risk of ischemic stroke or systemic embolism when compared with warfarin (3.2% versus 3.7%, P=0.43). Furthermore, rates of intracranial hemorrhage did not appear to differ between the 2 groups (1.0% versus 1.6%, P=0.10). Finally, a statistically lower rate of major gastrointestinal bleeding (1.9% versus 3.6%, P=0.003) and any major bleeding (2.9% versus 5.4%, P<0.001) was observed in the NOAC group. While the widely used Child-Pugh score was unable to be assessed in this study, outcomes may also have differed in relation to type and severity of cirrhosis. NOAC and warfarin therapy had no significant difference in outcomes in the alcoholic cirrhotic group. In the non-alcoholic cirrhotic group, however, NOAC therapy was associated with less bleeding compared to warfarin. The severity of cirrhosis was assessed by the presence of *ICD*-coded complications such as ascites and hepatic encephalopathy. Those with a lack of these complications, so-called nonadvanced cirrhosis, had a reduction in major bleeding and all bleeding risk with NOAC therapy. Advanced liver cirrhosis was associated with a reduction in intracranial hemorrhage in the NOAC group compared with warfarin.

This analysis by Dr Lee and colleagues is a welcome addition to the growing body of real-world data supporting the potential use of NOACs in patient subgroups underrepresented in the major randomized clinical trials. In general, the

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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J Am Heart Assoc. 2019;8:e012102. DOI: 10.1161/JAHA.119.012102.

subject of anticoagulation for AF in Asians is an important one for a multitude of reasons. From a population perspective, the burden of AF and its subsequent complications in Asia is of great concern. While the prevalence of this condition is lower, the absolute number of individuals living with AF in this region significantly outnumbers those in North America and Europe because of its populous nature.[6] Moreover, this discrepancy is expected to increase exponentially in coming decades as Asian societies continue to expand and undergo demographic transition.[6] However, there are unique and important subtleties that may alter the balance of efficacy and safety of anticoagulation in Asian populations.[7] First, Asians have a higher baseline risk of bleeding and intracranial hemorrhage.[7] Second, the rate of ischemic stroke appears be higher in Asians.[7] Third, the quality of warfarin anticoagulation seems to be less in Asians, as assessed by time in therapeutic range; this may be in part related to healthcare systems as well as genetic influences.[8] Finally, Asians more often have lower body weight, reduced creatinine clearance, lesser use of gastroprotectant drugs, and greater use of antiplatelet medications – factors that are all relevant to anticoagulant prescription.[7] In spite of these factors, there is an increasing wealth of recent information regarding the use of anticoagulation in Asians with AF. Reassuringly, stroke and bleeding risk can still be adequately assessed with the CHA_2DS_2-VASc and HAS-BLED scores, respectively.[7] From a practical point of view, the available observational and randomized data also support the general use of NOACs in preference to warfarin anticoagulation in Asian patients with AF.[9]

On one hand, the present study provides further evidence in support of NOAC use in Asian populations. However, on the other hand, the issue of comorbid cirrhosis confers another dimension on top of an already-existing degree of uncertainty. As a result, no specific recommendation is made in AF guidelines with regard to anticoagulation in patients with cirrhosis, except for the inclusion of liver disease as a component of the HAS-BLED bleeding risk score.[10,11] Yet, in addition to inducing a coagulopathy, thrombosis may also be facilitated in cirrhosis by lower levels of endogenous anticoagulants and higher levels of procoagulants.[12] Thus, patients with AF and cirrhosis are likely to be at both increased thrombotic and bleeding risk. Indeed, patients with cirrhosis appear to have a higher risk of ischemic stroke.[13] In the first instance, there is observational evidence to suggest that warfarin anticoagulation may be of benefit in AF patients with cirrhosis compared with no anticoagulation. An analysis from the same Taiwanese database has shown that warfarin use was associated with a lower ischemic stroke rate but similar intracranial hemorrhage rate compared with no antithrombotic or antiplatelet therapy in AF patients with cirrhosis.[13] A subsequent meta-analysis has been undertaken in AF patients with cirrhosis, of which notably 4 of the included 7 studies were in Asian populations; this provided further support that warfarin users had a lower risk of stroke compared with no anticoagulation (hazard ratio 0.58, 95% CI 0.35–0.96), albeit at a cost of greater bleeding.[14]

However, there has been up until this point a paucity of data on NOACs. All 4 major randomized controlled trials of NOACs excluded patients with active liver disease. Only 2 studies were included in the aforementioned observational meta-analysis that compared NOACs and warfarin, in which warfarin was found to have a higher bleeding risk (odds ratio 1.93, 95% CI 1.00–3.70).[14] Other reports have only included a few patients with AF and cirrhosis, suggesting similar or fewer bleeding risks with NOACs compared with warfarin, but of insufficient sample sizes to adequately compare thromboembolic outcomes.[15–18] Given the lack of clinical data, pharmacokinetic properties have provided reason to be cautious in the use of NOACs in liver impairment.[19] Body clearance, plasma protein binding, cytochrome P450 metabolism, and biliary clearance can all be affected in liver disease. Most NOACs have predominantly hepatic clearance (apixaban 75%, rivaroxaban 65%, edoxaban 50%, and dabigatran 20%). Furthermore, free drug fractions can increase when liver albumin synthesis is impaired because of high plasma protein binding (rivaroxaban 95%, apixaban 85%, edoxaban 55%, and dabigatran 35%). Moreover, cytochrome P450 enzyme activity and biliary excretion is decreased in liver impairment (apixaban and rivaroxaban are predominantly metabolized by cytochrome P450; dabigatran and edoxaban have minimal to none). Given these pharmacokinetic properties, cautious NOAC therapy has been thought until this time to be reasonable in Child-Pugh A liver disease, not recommended in Child-Pugh C liver disease, and variably recommended in Child-Pugh B liver disease.[19,20] The present study is thus an important step forward in providing much useful observational data regarding the safety of NOAC therapy in cirrhotic patients given the absence of randomized evidence. In a much larger sample size compared with prior clinical reports, the current findings suggest that low-dose NOAC anticoagulation may be a reasonable alternative to warfarin anticoagulation in Asian patients with AF and cirrhosis in terms of thromboembolism, and raise the possibility that they may even be superior from a bleeding point of view.

A number of limitations to this analysis are worthwhile mentioning, particularly as they may represent opportunities for future research. The findings of this data set cannot necessarily be extrapolated to non-Asian populations for reasons discussed above. In the absence of Child-Pugh scores, it is not known how many patients had Child-Pugh B or C liver disease, although 19% of patients on NOAC therapy had "advanced" liver disease in the form of complications. It is also of paramount importance to note that the vast majority of individuals in the NOAC group (>90%) were taking low-dose NOAC therapy; thus, any

conclusions regarding the safety of standard-dose therapy cannot be drawn. Moreover, further studies should ideally follow up patients for a longer period. Although the authors state that only some of the NOACs had risk reductions that were individually significant for bleeding end points, and other subpopulations (eg, type and severity of cirrhosis) had NOAC benefits on differing bleeding end points, the CIs were overlapping and interaction tests that were presented were nonsignificant, precluding conclusion on any true subgroup differences. Several factors relevant to the risk of both thromboembolic and bleeding complications were also not able to be assessed in this data set. The time spent in the therapeutic range for patients on warfarin was not available; it may be possible that benefits from NOACs are diminished with higher time in therapeutic range on warfarin. Other factors including blood pressure, renal function, and concomitant use of other medications were also not reported; these may increase bleeding risk and thus would be relevant to addressing this issue in the clinical setting. Study definitions were dependent on coding data, which may be subject to inaccuracies or differ from those used elsewhere, preventing between-study comparison. Finally, even though the present data may represent the best available evidence on NOACs in AF patients with cirrhosis, we cannot exclude the possibility of residual confounding in the absence of randomization, acknowledging that it is unlikely a large trial in this setting will be undertaken in the near future.

In conclusion, this large, observational study makes a significant contribution to the literature on the potential use of NOAC therapy in Asians patients with AF and cirrhosis. Low-dose NOAC therapy may be safe and efficacious in this setting in the short term, despite the known differences in risk profiles and outcomes in Asian populations with AF combined with the balance of thrombosis and bleeding in cirrhosis. Some additional areas of uncertainty remain unanswered, however, and we thus look forward to future studies that may help us continue to reduce the burden of AF and stroke in Asia and elsewhere.

Sources of Funding

Ms Gallagher is supported by a Leo J. Mahar Scholarship from the University of Adelaide. Dr Sanders is supported by Practitioner Fellowships from the National Health and Medical Research Council of Australia and the National Heart Foundation of Australia. Dr Wong is supported by a Mid-Career Fellowship from The Hospital Research Foundation and a Post-Doctoral Fellowship from the National Heart Foundation of Australia.

Disclosures

Dr Sanders reports having served on the advisory board of Biosense-Webster, Medtronic, St Jude Medical, Boston Scientific, and CathRx. Dr Sanders reports that the University of Adelaide has received on his behalf lecture and/or consulting fees from Biosense-Webster, Medtronic, St Jude Medical, and Boston Scientific. Dr Sanders reports that the University of Adelaide has received on his behalf research funding from Medtronic, St Jude Medical, Boston Scientific, Biotronik, and LivaNova. Dr Wong reports that the University of Adelaide has received on his behalf research, lecture, and/or travel funding from Novartis, Servier, Boehringer-Ingelheim, and Medtronic.

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Key Words: Editorials • anticoagulation • atrial fibrillation