Letters

TO THE EDITOR

Left Atrial Appendage Occlusion Devices Versus Pharmacological Agents for Stroke Prevention in Atrial Fibrillation

Testing the Noninferiority Margins

In studying the risk of stroke in patients with atrial fibrillation, the reports by Bajaj et al. (1) and Ruff et al. (2) represent the most updated analyses focused, respectively, on left atrial appendage occlusion devices (AODs) and pharmacological agents (i.e., warfarin and novel oral anticoagulants [NOACs]). According to the endpoint of stroke or systemic embolism, the crude event rates found in these analyses were: warfarin 1,107 of 29,229 (3.79%) (2); any NOAC 911 of 29,312 (3.11%) (2); and AODs 11 of 1,107 (0.99%) (1). The place in therapy of warfarin in this disease condition is well established, and the pros and cons of this drug are well known. On the other hand, the therapeutic placement of NOACs and, especially, AODs is still a matter of debate (2–4). Although no randomized trial has compared NOACs with AODs, the indirect comparison suggests no proof of difference (3), which is, however, an inconclusive result.

Despite the indirect nature of the comparison between AODs and NOACs, and the inherent limitations, maximizing the evidence currently available can be worthwhile, and in this framework, studying the noninferiority of AODs versus NOACs can be of interest.

Testing noninferiority is particularly straightforward when the information on margins is combined with standard Forest plots. Margins represent a threshold between clinically relevant incremental benefits and irrelevant ones, and can be retrieved from statistical power information of original trials.

We have applied this approach to evaluate the noninferiority of AODs versus NOACs in atrial fibrillation (endpoint: stroke or systemic embolism). The clinical material was the same as previously reported (1,2), the only difference being that the results were re-expressed as risk difference (RD) instead of relative risk. To evaluate this indirect comparison, we simply analyzed the crude event rates, and we then estimated the RD, along with its 95% confidence interval (CI), according to standard statistics (5). The noninferiority margin was set at the same value (RD = 2.5%) adopted in pivotal trials comparing NOACs versus warfarin (6). Hence, the Forest plot of our analysis contained a single dataset (i.e., the RD for the indirect comparison of AODs vs. NOACs) and the noninferiority interval for this parameter. This interval ranged from −∞ to +2.5%, whereas failure in demonstrating noninferiority corresponded to RD values exceeding +2.5%.

Our analysis determined a RD of −2.1% (95% CI: −2.7% to −1.5%) in favor of AODs in comparison with NOACs. The noninferiority criterion was largely satisfied because the 95% CI of RD remained entirely below the noninferiority margin at RD = +2.5%. In addition, these results also supported the conclusion that AODs are significantly superior to NOACs because the upper limit of the 95% CI did not reach the identity line (at RD = 0).

Of course, the safety of these interventions (1,2) is another important factor to appropriately define their therapeutic role. It should also be stressed that our statistical analysis was a very simplified one, since we directly relied on crude rates. Despite these limitations, a favorable therapeutic profile of AODs clearly emerges from the present analysis. Needless to say, randomized studies comparing AODs with NOACs are urgently required to shed light on this topic.

*Andrea Messori, PharmD
Valeria Fadda, PharmD
Dario Maratea, PharmD
Sabrina Trippoli, PharmD
*ESTAV Centro
Area Vasta Centro Toscana
Regional Health System
Via Guimaraes 9-11
59100 Prato
Italy
E-mail: andrea.messori.it@gmail.com OR andrea.messori@estav-centro.toscana.it

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Please note: The authors have carried out this study in the context of their activity at ESTAV Toscana Centro; ESTAV Centro belongs to the Italian national health system.
REPLY: Left Atrial Appendage Occlusion Devices Versus Pharmacological Agents for Stroke Prevention in Atrial Fibrillation

Testing the Noninferiority Margins

We thank Messori et al. for their interest in our recent systematic review of outcomes after implantation of percutaneous left atrial appendage (LAA) occlusion devices (1). The authors have used a novel statistical analysis to raise the possibility that LAA occlusion devices might be superior to newer oral anticoagulants (NOACs) in preventing stroke or systemic embolism. This is potentially a thought-provoking observation in favor of the efficacy of the percutaneous closure of the LAA.

The pivotal noninferiority randomized, controlled trials like RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) have tested whether individual NOACs were non-inferior to warfarin in preventing stroke or systemic embolism (2–4). The noninferiority margin in these trials was derived from an earlier meta-analysis of outcomes after administration of warfarin compared with placebo (5). The noninferiority margin was set at half the 95% confidence interval of the estimated effect of warfarin compared with placebo. Messori et al. have used this methodology in a unique quantitative-analytic framework to calculate the difference in outcomes between LAA occlusion devices and NOACs.

Although the superiority of LAA occlusion devices over NOACs is a possibility, the analysis described by Messori et al. is also somewhat provocative. We agree that this is a very interesting hypothesis and therefore would need to be verified in head-to-head randomized, controlled trials before widespread acceptability in clinical practice.

Akhil Parashar, MD  
Shikhar Agarwal, MD, MPH  
Navkaranbir S. Bajaj, MD  
E. Murat Tuzcu, MD  
*Samir R. Kapadia, MD  
*Department of Cardiovascular Medicine  
Heart and Vascular Institute  
Cleveland Clinic  
9500 Euclid Avenue, J2-3  
Cleveland, Ohio 44195  
E-mail: kapadis@ccf.org  
http://dx.doi.org/10.1016/j.jcin.2014.05.010

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