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Letter

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 pharmaceutical 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). However, no randomized trial has compared NOACs with AODs, and 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.

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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.
REFERENCES


