

Warfarin and aspirin for primary prevention in patients with heart failure in sinus rhythm

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Lala and co-workers (1) have argued that “while aspirin therapy decreases incident cardiovascular events, it also increases risk of major bleeding and hemorrhagic stroke”, and so “the benefit to risk ratio for aspirin use in primary prevention of cardiovascular events is less clear”. Heart failure (HF) in sinus rhythm is thought to be an indication for primary prevention not only with aspirin but also with warfarin, but this point has not been addressed in Lala’s article. Since aspirin and warfarin for patients with HF in sinus rhythm are an important therapeutic option particularly in the framework of individualized approaches, we have expanded the analysis of the evidence available in this area.

According to a meta-analysis based on 4 studies (2), aspirin and warfarin are equi-effective in reducing mortality in patients with HF in sinus rhythm. However, as compared with aspirin, the therapeutic profile of warfarin is more “unbalanced” because warfarin reduces to a greater extent than aspirin the incidence of ischemic stroke, but increases major bleedings. As a result, aspirin might be more appropriate in patients with high risk of bleeding, whereas warfarin could be preferred in patients with high thromboembolic risk.

To better define the place in therapy of these two agents, conducting further studies comparing warfarin *vs.* aspirin in unselected patients has been proposed (2); however, an open question remains on whether new studies in unselected patients can still be useful or, conversely, other comparative designs based on more selective enrolment criteria can be better. Therefore, we have addressed this issue by applying trial sequential analysis (TSA) (3,4).

Our TSA included the same 4 trials examined by Rengo

et al. (2) Our assumptions included two-sided testing, type 1 error =5%, power =80%. With respect to death rate from any cause, the intervention effect was set at relative risk reduction =15% with respect to 21% absolute event rate in the controls (equal to overall rate in the 4 aspirin arms). As usual, the main result of TSA was expressed through the graph of cumulative z-curve; the boundaries for concluding superiority or inferiority or futility in this graph were calculated according to the O’Brien-Fleming alpha-spending function. All calculations were carried out using a specific statistical software (TSA, User Manual for TSA, Copenhagen Trial Unit 2011, software downloadable at www.ctu.dk/tsa).

Our results are shown in *Figure 1*. Although the analysis estimated that 4,953 patients would be needed to conclusively demonstrate superiority or inferiority or futility, at the cumulative number of 3,663 patients (i.e., those enrolled in the 4 trials) the curve had already crossed the green boundaries and was in the futility area.

This finding is a sound proof that the results by Rengo *et al.* (2) are conclusive, but-more importantly-specific clues can be obtained from our results about the optimal design of future trials in this area. In fact, further comparative studies in unselected patients seem to be useless because of this statistical demonstration of futility; on the other hand, there seems to be the need for further comparative studies based on the enrolment of select subpopulations (e.g., those with high risk of bleeding or with high thromboembolic risk). In this framework, appropriate comparators might include not only warfarin and aspirin, but also the novel oral anticoagulants because of their potential advantages in patient management (5).

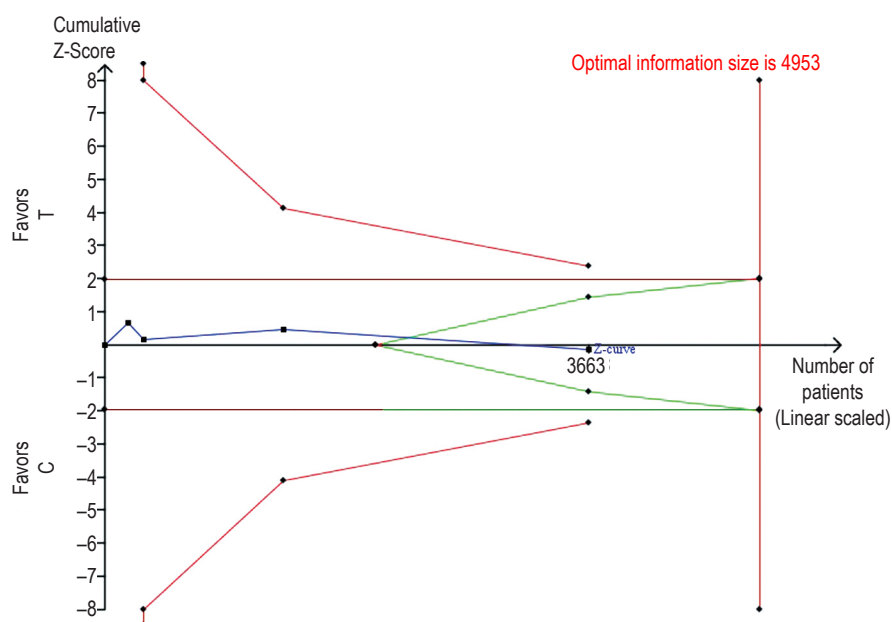


Figure 1 Trial sequential analysis based on 4 randomized trials comparing warfarin *vs.* aspirin. In the z curve (represented in blue), individual trials correspond to individual segments; trials are plotted in chronological order (from left to right). The x-axis indicates the cumulative number of patients; the starting point of the z-curve is always at $x=0$, i.e., inclusion of no trials. Abbreviations and symbols: T, treatment arm (warfarin); C, control arm (aspirin); red lines are the boundaries for superiority or inferiority while green lines are the boundaries for futility; futility is proof of no effectiveness (i.e., demonstration of both non-superiority and non-inferiority)

In conclusion, designing new trials in this area is becoming increasingly complex, and so the identification of futile designs for future primary prevention studies can be of value. On the other hand, if future studies in primary prevention are aimed (as indicated by our analysis) at more selective uses of known agents, this approach will also contribute to improve individualisation of treatments in this area.

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