Figure 1. Kaplan-Meier survival curves free from total mortality (A and B) and cardiac mortality (C and D) according to the quartiles of (A and C) EuroSCORE II (group I, 0 to 0.93; group II, 0.93 to 1.322; group III, 1.322 to 2.425; and group IV, >2.425) and (B and D) old logistic EuroSCORE (group I, 0 to 1.614; group II, 1.614 to 3.048; group III, 3.048 to 6.35; and group IV >6.351).

Risk of Myocardial Infarction With Oral Direct Thrombin Inhibitors: Trial Sequential Analysis Based on Two Published Data Sets

Oral direct thrombin inhibitors (DTIs) have been postulated to increase the risk of myocardial infarction (MI). The meta-analysis by Artang et al. has exhaustively explored this topic by addressing 2 separate questions: (1) Is there an excess rate of MI that can be attributed to DTIs? (2) Does warfarin reduce the incidence of MI to a greater extent than nonwarfarin anticoagulants? Based on 2 separate data sets of randomized controlled trials, Artang et al. have interpreted their findings by concluding that DTIs are associated with an increased risk of MI and that warfarin does not differ from the other anticoagulants in the risk of MI.
We have carried out a trial sequential analysis (TSA) to reexamine the same 2 data sets published by Artang and coworkers. Based on our results, our conclusions are quite different from those of these investigators because (1) the increased risk of MI from DTIs does not seem to be conclusively demonstrated; furthermore, the number of patients enrolled in the trials conducted thus far is nearly 5 times less than the ideal sample required to generate conclusive results.

A Cumulative Z-score

B

RRR > 25% = 18,328

RRR = 25%, control rate = 1.3% = 91,560

Number of patients (Linear scaled)

Figure 1. Risk of MI: TSA of 10 RCTs comparing oral DTIs with warfarin, the first data set (A), and 8 RCTs comparing nonwarfarin anticoagulants with warfarin, the second data set (B). The expected RRR was assumed to be 25% in both analyses. In the z curve (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, that is, inclusion of no trials. According to the TSA algorithm, the information available in (A) was insufficient to determine the boundaries of futility. Red lines are the boundaries for superiority or inferiority; green lines are the boundaries for “futility” (i.e., “proof of no difference”); and the red vertical lines on the right indicate the estimate of the optimal cumulative sample size. The complete references for the RCTs can be found in the study by Artang et al. C = control arm (warfarin); RCT = randomized controlled trial; RRR = relative risk reduction; T = treatment arm (oral DTIs in [A], nonwarfarin anticoagulants in [B]).

determined 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, Copenhagen, Denmark, software downloadable at www.ctu.dk/tsa).

Figure 1 summarizes the results of our 2 TSAs. In the first data set, although the z curve confirmed the hypothesis that the risk of MI might be increased with DTIs, this hypothesis remained quite far from a conclusive demonstration; in fact, the z curve remained far from the boundaries of inferiority and, more importantly, the optimal information size was estimated at 185,828 patients, which is much more than the cumulative number of patients studied thus far (n = 39,357). Hence, many more data are needed to settle this question. In the second data set, the z curve clearly demonstrated the proof of no difference; interestingly enough, the findings from this second TSA were conclusive because although the available patients (n = 69,615) were fewer than the optimal information size (n = 91,560), the last point of the z curve was clearly within the boundaries of futility; so, there is no need to collect more data to settle this specific therapeutic question.

In summary, the main result of our reanalysis is that the hypothesis that DTIs increase the risk of MI has not been conclusively demonstrated; interestingly enough, the findings from this second TSA were conclusive because although the available patients (n = 69,615) were fewer than the optimal information size (n = 91,560), the last point of the z curve was clearly within the boundaries of futility; so, there is no need to collect more data to settle this specific therapeutic question.

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Reply

Messori et al analyzed the raw data from our study using an alternative software titled trial sequential analysis (TSA; Copenhagen Trial Unit, Copenhagen, Denmark) and observed different results compared with our original meta-analysis in which the Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, New Jersey), was used. Based on their analysis, “the increased risk of myocardial infarction (MI) from oral direct thrombin inhibitors (DTIs) did not seem to be conclusively demonstrated. And the similar rates of MI observed between warfarin and non-warfarin anticoagulants not only indicated no proof of difference but also demonstrated the proof of no difference.”

In response, we are relieved that the result of the second meta-analysis confirmed the lack of protective effect of warfarin against MI compared with non-warfarin anticoagulants with the use of TSA software.

As for the primary meta-analysis, it is important to understand that we are dealing with a meta-analysis for the purpose of hypothesis generation using trials in which MI was not the primary end point. We therefore did not declare the data on the association of DTIs and MI conclusive as such a statement cannot only be based on a meta-analysis, and should be further examined in a randomized trial with MI as the primary end point. This study was inspired by the observations from several randomized trials showing increased rates of MI associated with the use of DTIs including the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) with Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY) and Thrombin Inhibitor in Venous Thromboembolism (THRIVE) trials. Besides the clinical observation from these randomized trials, there seems to be additional laboratory evidence that may support a hypothesis that certain mechanisms related to the direct thrombin inhibition may be the cause of these thromboembolic events, particularly at low concentrations of the direct thrombin inhibitor.

Messori et al raise an important point regarding the methodology of meta-analysis in general. The TSA methodology is based on the principle that when one is taking multiple peeks at the data, or rerunning a meta-analysis every time a new study comes out, there should be an adjustment of the parameters. Furthermore, a sample size is defined before proceeding with the meta-analysis to consider the study statistically valid.

Their critique, however, is not only directed toward our results but also toward most meta-analysis studies published in the contemporary medical literature. Very few of those studies would pass optimum sample size requirement set by TSA. TSA methodology provides a very conservative approach toward meta-analysis. For association of DTIs and MI, Messori et al calculated the optimal sample size of more than 185,000 subjects to achieve a power of only 80% compared with almost 40,000 subjects that were included in our original analysis. It is obvious that using a mammoth sample size would reduce the risk of false-positive results, but this comes at the price of potentially delaying a possible implementation of an intervention toward harmful effects of a drug for several years. A counter argument can be made when dealing with rare harmful cardiovascular events associated with commonly used drugs. In those circumstances, a more aggressive approach may be preferred such as application of fixed-effect model even in the presence of significant heterogeneity of the data may be necessary to prevent experiences such as the late withdrawal of rofecoxib from the market due to significantly increased risk of cardiovascular events.

Our meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines that is most commonly used by investigators for the performance and publication of meta-analysis. The conditions for application of the fixed-effect model in the primary meta-analysis were met. The conclusion reached regarding association of DTIs and coronary events is in concordance with other meta-analysis studies of association of dabigatran and risk of coronary events. Our study extends this observation beyond dabigatran and opens the question of possible problems with univalent direct thrombin inhibition. This information may be helpful for a more critical view of novel anticoagulants for clinicians who deal with daily patient care and investigators who plan to design future studies with this class of agents.