Biostatistics Seminar

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Assessing the cardiovascular risk of anti-diabetic therapies in patients with type 2 diabetes mellitus

Recent guidance from the United States Food and Drug Administration (US FDA) and European Medicines Agency present recommendations to assess cardiovascular (CV) safety for non-insulin anti-diabetic therapies in patients with type 2 diabetes mellitus (T2DM). In particular, the risk of major adverse CV events, which includes CV death, non-fatal myocardial infarction and non-fatal stroke events, is assessed in two stages in the US FDA guidance. Stage 1 is a pre-market evaluation of the novel compound to placebo testing whether the upper bound of the 95% confidence interval of the hazard ratio is < 1.8. Assuming the drug application is otherwise acceptable, if the CV criteria is met the sponsor obtains full marketing approval for the new drug. In Stage 2, the sponsor must evaluate the post-market criteria testing the hazard ratio against a more stringent upper bound of 1.3. This approach is to strike a balance between providing evidence on cardiovascular safety to reassure patients and excessive delay of novel therapies reaching the marketplace. To understand the impact of FDA guidance on T2DM development programs, we reviewed drug applications for treatments approved by the US FDA during 2002-2014. In this talk, we summarize the CV assessment strategies applied in practice, and describe the advantages and disadvantages of individual methods. The implications of the above regulatory framework, particularly in regards to the size of the safety database and the confidentiality of interim results, are discussed. This work is presented on behalf of the Safety Working Group of the Biopharmaceutical Section of the American Statistical Association.

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