

The PPI Risk Explorer, Its Development and Application in Assessing the Interaction of Drugs to Treat Osteoporosis and Proton Pump Inhibitors (PPIs) Use in the Risk of Osteoporosis Related Adverse Events

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Abstract

Reports of paradoxical atypical femoral fractures and other osteoporosis related adverse events in patients that receive drugs to treat osteoporosis, including bisphosphonates, to prevent vertebral and/hip fractures promoted this investigation to explore the interaction of concomitant PPI use with therapy of drugs to treat osteoporosis. The most frequent dose limiting adverse effects (AEs) of bisphosphonate use are nausea and gastrointestinal intolerance; proton pump inhibitors (PPIs) are frequently used drugs to mitigate these adverse events.

We developed a tool to assess the risk of adverse events from therapy using drugs to treat osteoporosis in relation to exposure to PPIs that can be applied to a trial database that include placebo controlled studies with at least 3 years of total study drug exposure. The tool has a trial selection function that can separately display one or multiple trials and show specific adverse events in 4 groups. The four groups are 1) treatment with concomitant PPIs; 2) treatment without concomitant PPIs; 3) placebo with concomitant PPIs; and 4) placebo without concomitant PPIs. The statistical analysis results are displayed in a pixel graph column, which reports whether or not an AE is reported. The relative risk (RR) of AEs and the AE correlations are displayed graphically and numerically. RRs and associated confidence intervals (CIs) can also be displayed in a bar chart display function. The temporal relationship of AEs relative to therapy is displayed in a time line graph which enables users to examine one or more AEs in greater detail. The poster will describe the methodology of tool development, trial selection, and analytical approach, and will provide selected examples to illustrate tool functionality. The tool can be applied to any clinical trial that has standardized datasets, with trial drugs only or with trial drugs and concomitant medicines.

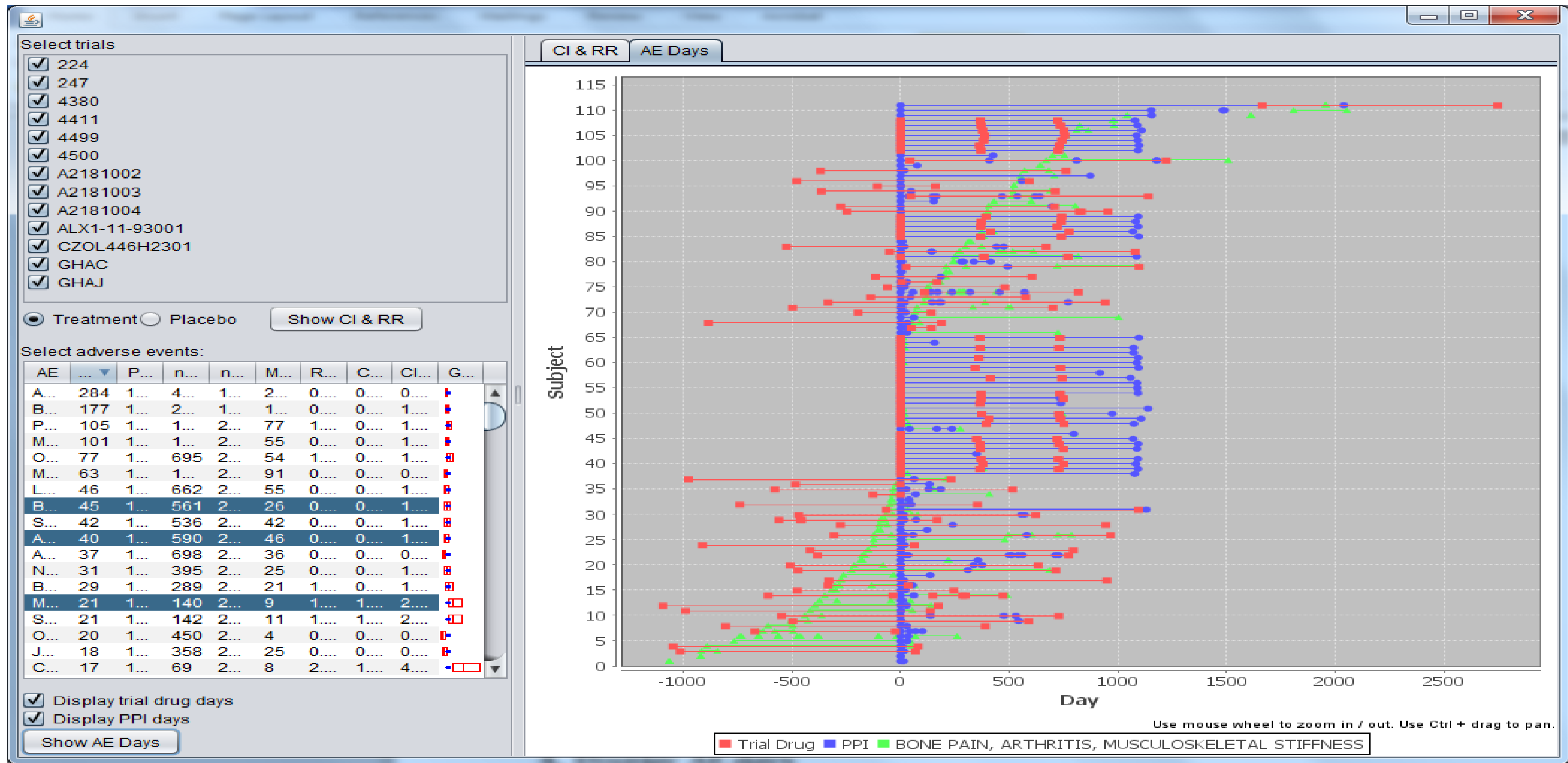
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Introduction

In this study we have built a legacy database, ARRA_PCOR (American Recovery and Reinvestment Act - Patient Centered Outcome Research) PPI database, that contains large datasets in the standardized format of Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM). The datasets include exposure information from 13 clinical trials, which provide a unique (large and standardized) data to assess the adverse events of PPIs. We developed GUI tools that enable us to answer the following questions: 1) Does the concomitant use of PPIs affect the efficacy of the drugs that treat osteoporosis? 2) Does the use of some or all PPIs in the ARRA_PCOR database increase the risk of osteoporosis in women at a significant level? 3) Does the risk of osteoporosis with PPIs differ for women by age or race strata? 4) Are there other safety issues associated with the use of PPIs? Besides, the tool can allow user to select trials and the AEs being interested and can display the relationship between the exposure times of trial drug and concomitant drug and the duration of AEs, regardless how large the trial is. The user can use the tool to get basic and advanced statistical analysis results such as RRs and CIs that are conveniently displayed in graphs and tables. This poster introduces this tool and its use.

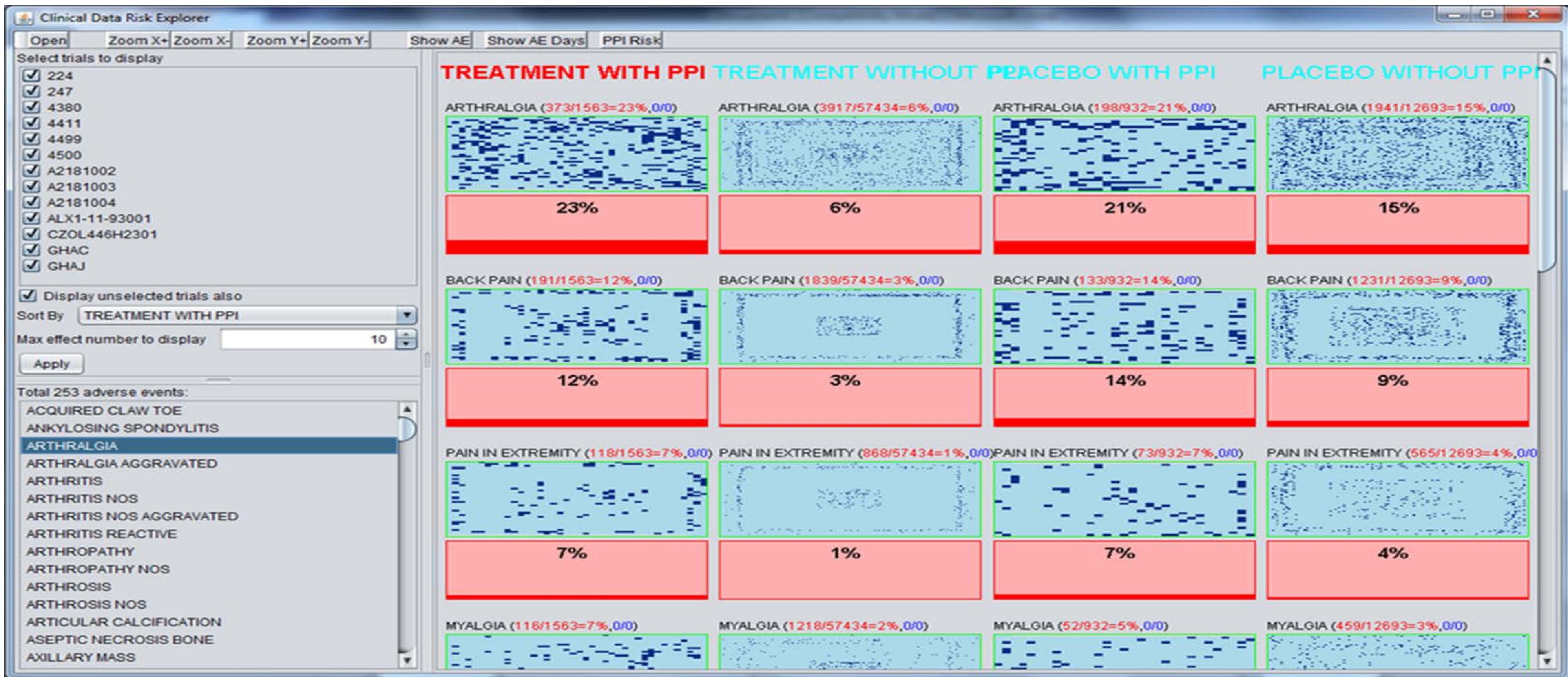
Examine temporal information using TimeLine Graph

The timeline graph allows users to examine AEs of interest in further detail. Select one or more AEs from the table of the Bar Chart window and click the “AE days” tab to open the Timeline graph for the selected AEs. In the graph, the time periods a patient taking PPI, taking the drug of the trial, and having AEs are represented by a blue line, a red line, and a green line, respectively. The lines for the same patients are adjacent to each other. Each patient has her/his own time line (from left to right). The time lines of different patients are aligned so that the starting times of PPI taking have the same X position (marked by 0 in the X axis). The patients are sorted by the starting time of the AEs. This graph allows users to examine details of the durations of the PPI taking, AEs, and drug taking, which are hidden in the statistical values such as relative risk. According to the patterns observed from the graph, the users can adjust the calculation of the relative risks for more reliable results.



Examine Relative Risk of AEs and AE Correlations Using the Pixel Graph Window

The pixel graph window allows users to examine the relative risks of PPI on AEs and the correlations among the AEs. It consists of a toolbar, a trial selector, an adverse event (AE) list, and pixel graphs (the blue windows). The trial selector on the top left allows users to select one or more trials to be analyzed. Subjects of the selected trials are displayed in the pixel graphs displayed on the right of the window. They are divided into four groups, namely subjects with treatment and PPI, subjects with treatment without PPI, subjects taking placebo and PPI, and subjects taking placebo without PPI. Each group is displayed using a column of pixel graph. Each pixel graph displays whether or not the subjects reported an AE. In particular, each subject is represented by a small block and its color is dark blue/light blue if the subject has/hasn't the AE. The positions of the same subject in all pixel graphs in the same column are the same and users can assign the positions according to different criteria. Therefore, the correlation of AEs can be identified by comparing the texture of the pixel graphs. The pixel graphs of the same AE on different groups are placed in the same row for comparison. For better examination of the relative risk, a histogram is displayed under each pixel graph, with shows the ratio of subjects with the AE in the group. By comparing the histogram heights of the treatment with PPI group with the treatment without PPI group as well as those of the placebo with PPI group and the placebo without PPI group, users can learn the relative risk of PPI on the AE examined. In addition, the numerical values of the relative risks are displayed after the AE names in the labels of the pixel graphs. Users can also select AEs of interest from the AE list on the bottom left of the window and examine only their pixel graphs.



Examine Relative Risk & Confidence Interval of AEs in the Bar Charts window

The Bar Charts window provides a more straightforward way to examine relative risks and confidence intervals than the pixel graphs. Clicking “Show Risk Bar Charts” in the toolbar of the pixel graph window will open the Bar Charts window. The trial selector is on the top left of the window. On the bottom left is a table shows the AE names, the relative risks of the AEs in the trials selected, the numbers used in the relative risk calculation, and small bars graphically display the relative risks and their confidence intervals. On the right is the bar chart display. It provides a compact display of the relative risks and their confidence intervals of a large number of AEs and allows easy comparison. The three short vertical lines in each bar represent the lower/upper bound of the confidence interval and the relative risk of each AE displayed. The AEs are sorted by the lower bound of the confidence interval.

