Documentation of study medication dispensing in a prospective large randomized clinical trial: Experiences from the ARISTOTLE Trial

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Background In ARISTOTLE, apixaban resulted in a 21% reduction in stroke, a 31% reduction in major bleeding, and an 11% reduction in death. However, approval of apixaban was delayed to investigate a statement in the clinical study report that "7.3% of subjects in the apixaban group and 1.2% of subjects in the warfarin group received, at some point during the study, a container of the wrong type."

Methods Rates of study medication dispensing error were characterized through reviews of study medication container tear-off labels in 6,520 participants from randomly selected study sites. The potential effect of dispensing errors on study outcomes was statistically simulated in sensitivity analyses in the overall population.

Results The rate of medication dispensing error resulting in treatment error was 0.04%. Rates of participants receiving at least 1 incorrect container were 1.04% (34/3,273) in the apixaban group and 0.77% (25/3,247) in the warfarin group. Most of the originally reported errors were data entry errors in which the correct medication container was dispensed but the wrong container number was entered into the case report form. Sensitivity simulations in the overall trial population showed no meaningful effect of medication dispensing error on the main efficacy and safety outcomes.

Conclusions Rates of medication dispensing error were low and balanced between treatment groups. The initially reported dispensing error rate was the result of data recording and data management errors and not true medication dispensing errors. These analyses confirm the previously reported results of ARISTOTLE. (Am Heart J 2013;166:559-565.e1.)

The Apixaban for Reduction In STroke and Other ThromboembolLic Events in Atrial Fibrillation (ARISTOTLE) trial was designed to establish the efficacy and safety of apixaban compared with warfarin in patients with atrial fibrillation (AF) at risk for stroke. The design and results have been published.[1,2]

In ARISTOTLE, apixaban resulted in a 21% reduction in stroke or systemic embolism, a 31% reduction in major bleeding, and an 11% reduction in mortality.[2] Based on these results and supporting findings from AVERROES,[3] Bristol-Myers Squibb and Pfizer submitted a New Drug Application for apixaban to the US Food and Drug Administration (FDA) in September 2011 to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF. Approval in the United States was delayed twice: first in March 2012, requiring a major amendment that extended the review cycle by 3 months, and second by a Complete Response Letter in June 2012 requesting additional information on potential study medication errors and "other data management and verification issues" (online Appendix Supplementary Table).[4] The questions around study medication errors were prompted by the following statement in the ARISTOTLE clinical study report to the FDA: "The difference in the proportion of subjects with relevant or significant (protocol) deviations is driven by error in treatment assignment where 7.3% of subjects in the apixaban group and 1.2% of subjects in the warfarin group received, at some point during the study, a container of the wrong type." This statement raised concerns that the rate of study medication error might be

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higher than expected and, because of differences across treatment groups, might reflect bias.

The delay in the approval of apixaban has prompted questions about the nature of issues raised by the FDA.[5] The purpose of this article is to describe the study medication dispensing issue in ARISTOTLE and present the additional investigations and analyses that were performed and submitted to health authorities to address it.

Methods

ARISTOTLE was a randomized, double-blind, double-dummy, active-controlled international clinical trial.[1] A total of 18,201 patients with AF and at least 1 additional risk factor for stroke were randomized to apixaban 5 mg twice daily (or 2.5 mg in selected patients) or adjusted-dose warfarin to achieve a target international normalized ratio (INR) of between 2 and 3. The primary outcome was stroke or systemic embolism.

There was a comprehensive data and on-site monitoring program. Investigators were trained during on-site initiation visits and at regional investigator meetings, and trained monitors visited sites at regular intervals. Major areas of focus for quality during the trial included ensuring adequate power with sufficient primary outcome events, maintaining the study blind, systematic and complete ascertainment and adjudication of outcome events, minimizing premature study medication discontinuation, minimizing loss to follow-up and withdrawal of consent, and ensuring high-quality INR control in the warfarin arm.

Study medication dispensing in ARISTOTLE

Containers with blinded apixaban 5.0 mg and 2.5 mg and warfarin 2.0 mg were shipped in bulk to sites. Treatment assignment was made by an interactive voice response system (IVRS) that specified a unique 6 digit number for each container. Those randomized to apixaban received 1 container with active apixaban and 1 with placebo warfarin; those randomized to warfarin received 1 container with placebo apixaban and 1 with active warfarin. Apixaban (and apixaban placebo) containers were distributed every 3 months. Warfarin (and warfarin placebo) containers were distributed more frequently as required based on warfarin dose adjustment.

When the containers were dispensed, a tear-off portion of the label containing the unique 6-digit number was removed and retained with the participant's source documents. The 6-digit number was recorded on paper study medication log forms at the site and also recorded in the electronic case report form (eCRF) at the time of initial dispensing, verified at each follow-up visit, and confirmed and recorded in the eCRF when the containers were returned. Thus, each dispensed study medication container number was documented as many as 9 times in a variety of paper and electronic locations (Table I). The type font on the label was smaller on the warfarin containers than on the apixaban containers.

Approximately 9 million data points were collected in the study medication module of the eCRF, including >1 million study medication container numbers. During site visits, monitors confirmed that the container number on the tear-off portion of the container labels matched both the number assigned by the IVRS and the number recorded in the eCRF. For both apixaban and warfarin containers, electronic data validation checks were programmed to assess whether container numbers entered in the eCRF were within a valid number range and whether the number was a duplicate of a previously entered number. Programmed listings were run to identify potential data entry errors, primarily in the container dispensed fields, for apixaban and warfarin containers. Electronic data validation checks were programmed to confirm that returned container numbers matched dispensed container numbers; however, these were only run for apixaban (and apixaban placebo) and not for warfarin (or warfarin placebo) containers. The decision to perform more limited data validation checks on the warfarin containers was because warfarin was carefully monitored pharmacodynamically via INR monitoring, whereas there was no such monitoring for apixaban.

Table I. Study medication dispensing in ARISTOTLE

1. Ascertainment of container number from IVRS
   - Every 3 m for apixaban (apixaban placebo)
   - Up to monthly for warfarin (warfarin placebo)
2. Selection of appropriate container from among apixaban or warfarin study medication supply at site
3. Removal of tear-off portion of container label (including container number) and its retention as a source document at the site
4. Dispensation of container to intended study participant
5. Recording dispensed container number in master and individual participant drug log and manual entry of container number into eCRF
6. Verification of container number that participant has compared with container number in eCRF during interim visits
7. Manual reentry of container number into eCRF upon return of container to site
8. Electronic data validation checks to ensure that interim visit and returned container number match dispensed container number*

*Step 8 was performed for apixaban and apixaban placebo containers but not for warfarin or warfarin placebo containers.

Original study report analysis of study medication dispensing errors

Because the purpose of the original analysis described in the study report was to exclude the possibility that deficiencies in study conduct could affect the study results, a conservative approach was taken to counting errors. All container numbers entered into the eCRF were used, and any container number for an active treatment of the incorrect type was considered a dispensing error even if all other eCRF entries for this dispensation corresponded to the correct treatment type. Incorrect placebo container numbers were not counted in this analysis. Based on these analyses, it was reported that 7.3% of participants assigned to apixaban and 1.2% assigned to warfarin received a container of the wrong type at some point during the study.

Additional study medication label analysis

Analysis of the tear-off portion of the study medication labels retained by the sites with the participant's source documents provided a mechanism to determine the true rate of study medication dispensing error in the trial. In March 2012, at the request of the European Medicines Agency, 12% of all study medication labels were collected from a randomly selected