Response to Letter Regarding Article, "Efficacy and Safety of Apixaban Compared With Warfarin at Different Levels of Predicted International Normalized Ratio Control for Stroke Prevention in Atrial Fibrillation"

We thank Drs Replogle and Pittman for their comments on how to best report and refer to the results of prospective, randomized, clinical trials. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial was a prospective, randomized, clinical trial in which the patients were recruited over more than a year and for which the follow-up time was predefined to continue until a prespecified number of primary outcome events were accrued. The start of recruitment of patients from different countries occurred at different time points who will have different exposure to study drugs at the end of the study. Therefore the trial cohort will have a variable composition of patients and a corresponding variability in event rate during the course of the trial. The statistical analyses of the primary and all secondary outcomes were performed by the Cox proportional hazards modeling, including all randomized patients (intention-to-treat) and all events from randomization until the efficacy cutoff date. The results obtained from such analyses are hazard ratios, confidence intervals, and corresponding significance levels assuming proportional hazards during the duration of the trial regardless of the eventual variability in absolute event rates over time. Therefore the most appropriate and correct presentation of the result will be the relative reduction in event rates with apixaban as compared with warfarin as presented by the hazard ratio or the corresponding relative percentage difference. As shown in the main ARISTOTLE article as well as in several ARISTOTLE substudy articles[1–5] the Cox proportional hazards modeling shows consistent results in a large number of subgroups with different absolute event rates. Thus, when referring to the treatment effects of apixaban as compared with warfarin, the relative benefits seem to be the most appropriate way to report the results because these data reflect what can be expected in all populations.

The published scientific reports from the ARISTOTLE trial include the numbers of randomized patients, numbers and proportions of events, hazard ratios, confidence intervals, and *P* values for different events during follow-up. When comparing apixaban with warfarin in the overall ARISTOTLE trial population, the absolute event rates, the relative and absolute risk reductions, and the numbers needed to treat to prevent one event per 100 patient years of follow-up are as follows:

- for stroke and systemic embolism 1.27 versus 1.60, 21%, 0.33 and 301
- for all-cause death 3.52 versus 3.94, 11%, 0.41 and 241
- major bleeding 2.13 versus 3.09, 31%, 0.96 and 105
- intracranial bleeding 0.33 versus 0.80, 58%, 0.47 and 213
- all the above events 6.13 versus 7.20, 15%, 1.07 and 94

As emphasized in several of the substudy articles, including the time in therapeutic range article,[5] the absolute event rates and the numbers needed to treat will be higher in patients at higher risk (eg, at previous stroke, higher CHADS-scores, higher age, renal dysfunction, lower time in therapeutic range in the warfarin arm, etc).[1–5] Thus, the estimates of absolute and relative benefits provide complementary information. However, the most reliable and consistent estimate of the treatment effect in all subgroups is the relative benefit in the total trial.

Disclosures

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References

1. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
2. Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, Alings M, Goto S, Lewis BS, Rosenqvist M, Hanna M, Mohan P, Alexander JH, Diener HC; ARISTOTLE Committees and Investigators. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol*. 2012;11:503–511.
3. Lopes RD, Al-Khatib SM, Wallentin L, Yang H, Ansell J, Bahit MC, De Caterina R, Dorian P, Easton JD, Erol C, Ezekowitz JA, Gersh BJ, Granger CB, Hohnloser SH, Horowitz J, Hylek EM, McMurray JJ, Mohan P, Vinereanu D, Alexander JH. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. *Lancet*. 2012;380:1749–1758.
4. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, Keltai M, Lanas F, Lopes RD, Lopez-Sendon J, Granger CB, Wallentin L. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012;33:2821–2830.
5. Wallentin L, Lopes RD, Hanna M, Thomas L, Hellkamp A, Nepal S, Hylek EM, Al-Khatib SM, Alexander JH, Alings M, Amerena J, Ansell J, Aylward P, Bartunek J, Commerford P, De Caterina R, Erol C, Harjola V-P, Held C, Horowitz JD, Huber K, Husted S, Keltai M, Lanas F, Lisheng L, McMurray JJV, Oh B-H, Rosenqvist M, Ruzyllo W, Steg PG, Vinereanu D, Xavier D, Granger CB. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation clinical perspective. *Circulation*. 2013;127:2166–76.