Appendix 4: Adequate duration of therapy with dual antiplatelet therapy

Methods

The guideline panellists, by visual inspection of the survival curves of the individual studies, hypothesized that most of the difference between DAPT and ASA in stroke occurs up to day 10, a smaller difference between days 11 and 21, and that there is no difference between the DAPT and ASA after day 21. They therefore constructed the intervention and comparator for the second PICO question as clopidogrel for 10 to 21 days versus clopidogrel for 22 to 90 days. They also hypothesized that the relative increase in bleeding risk would be similar between the intervention and comparator groups across the entire time frame.

Using the stroke and major bleed probabilities plotted within the Kaplan Meier curves of the two large eligible trials[1 2], we utilized the DigitizeIt software (DigitizeIt, Braunschweig, Germany) to obtain the survival probabilities for both stroke and bleeding. For the POINT trial we used the entire 90 days of follow-up; for the CHANCE trial, because participants randomized to DAPT were prescribed DAPT for only 21 days, we used data only up to day 21.

We then calculated the individual time-to-event patient data[3]. We compared the original Kaplan Meier curves with the reconstructed Kaplan-Meier curves visually to ensure accuracy of the simulated individual patient time-to-event data, as well as the calculated hazard ratios and their CIs.

We generated odds ratios for each period by conducting logistic regressions to test the effect of DAPT vs. ASA (independent variable) on stroke and bleeding (dependent variables) for days 0 to 10, 11 to 21, and 22 to 90. We also generated pooled Kaplan-Meier curves for each of these time periods.

To calculate absolute effects, we utilized the simulated individual patient data to compare the risk difference for DAPT vs ASA up to day 10, from day 11 to 21, and from 22 to 90 days.

Results

Figure 1 shows the pooled Kaplan-Meier curves for ischaemic stroke and moderate or major bleeding for patients randomised to DAPT or ASA for days 0-10, days 11-21 and days 22-90. Within the first 10 days, patients randomized to DAPT had a 2% lower risk of stroke compared to those randomized to ASA alone (odds ratio [OR] 0.64, 95% CI 0.55 to 0.76). The difference between the groups in risk of stroke was both smaller for days 11 to 21 (OR 0.73, 95% CI 0.47 to 1.13) and the confidence interval included both an increase and decrease in stroke. The point estimate for risk of stroke for days 22 to 90 suggested an increase in risk with clopidogrel, though the confidence interval included a small decrease (OR 1.47, 95% CI 0.84 to 2.56). The risk of bleeding was higher in patients randomized to DAPT during all of the time periods, with similar magnitudes in relative terms: days 0 to 10, OR 1.71, 95% CI 1.02 to 2.86; days 11 to 21, OR 2.70, 95% CI 0.84 to 6.44; and days 22-90, OR 2.20, 95% CI 0.83 to 5.78. A longer duration of DAPT did not result in an important reduction of ischaemic stroke but did cause a small increase in risk of moderate to major bleed.

Discussion

Most of the benefit in terms of strokes prevented with DAPT occurs within the first 10 days after stroke; evidence strongly suggest no important reduction – and likely no reduction at all - after

21 days. On the other hand, DAPT consistently increases the risk of bleeding for the duration that the patients remained on DAPT.

References:

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3. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9. doi: 10.1186/1471-2288-12-9 [published Online First: 2012/02/03]

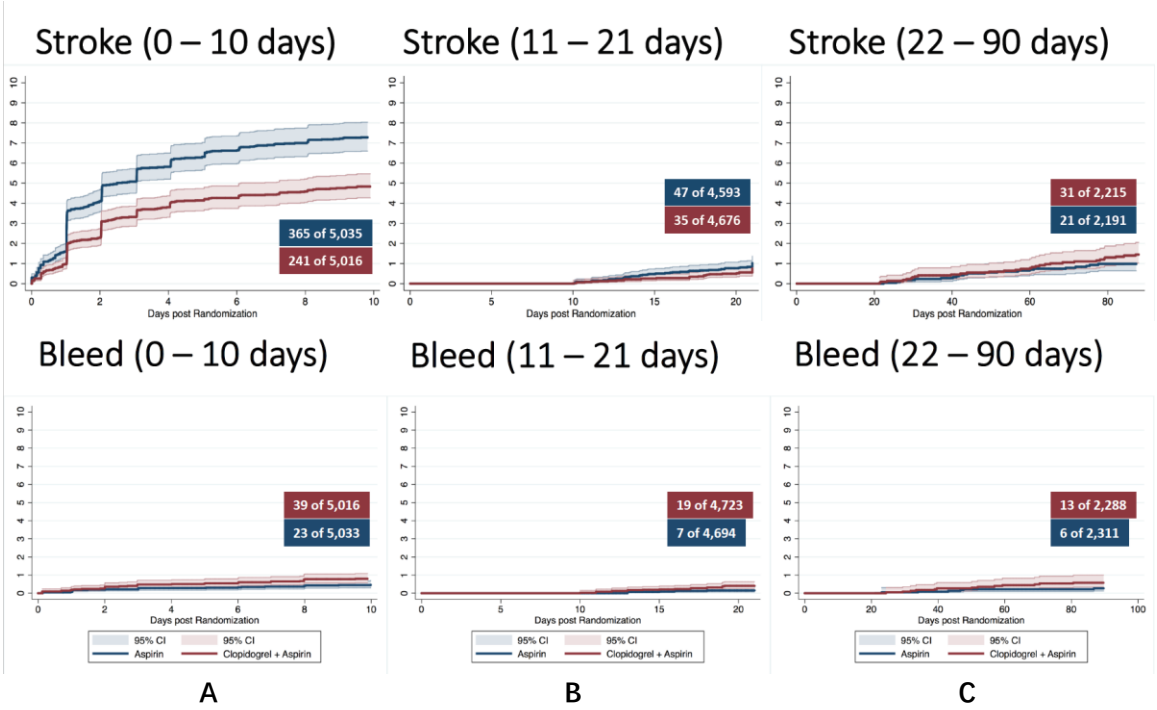

Figure 1. A – Time to event curves for ischaemic stroke and major bleeding in patients treated with dual anti platelet therapy (DAPT) or aspirin (ASA), up to 10-days after randomization. B - Time to event curves for ischaemic stroke and major bleed for days 11 to 21; limited to patients who did not have an ischaemic stroke or major bleed within the first 10 days, respectively. C Time to event curves for ischaemic stroke and major bleed for days 22 to 90; limited to patients who did not have an ischaemic stroke or major bleed within the first 21 days, respectively.