**Appendix 3: The definition of bleeding events and the stroke subtypes in the three included trials**

**FASTER**[1]

Severe bleeding defined as life threatening, resulting in haemodynamic compromise or hypovolemic shock, requiring inotropic support or other means to maintain cardiac output, requiring blood transfusion of more than 2 units of packed red blood cells, or associated with a fall in haemoglobin greater than or equal to 5 g/L;

Moderate bleeding defined as bleeding requiring a transfusion of 2 units of packed red blood cells or less, not severe as defined above, nor associated with a fall in haemoglobin of less than 5 g/L;

Mild bleeding defined as bleeding not requiring transfusion, not causing haemodynamic compromise, usually including haematoma, subcutaneous bleeding, oozing from puncture sites, and may require modification of drug regimen

Asymptomatic bleeding defined as bleeding that results in no symptoms.

The authors presented the distribution of stroke subtype according to different arms. After calculation the distribution is: Cardioembolic (6.6%); lacunar (28.8%); large artery (24.0%); unknown (36.7%); other (1.3%). The authors did not examine the treatment effect in the different stroke categories.

**CHANCE**[2]

Severe bleeding defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention;

Moderate bleeding defined as bleeding that required transfusion of blood, but did not lead to hemodynamic compromise requiring intervention;

Mild bleeding defined as bleeding not requiring transfusion and not causing hemodynamic compromise (e.g., subcutaneous bleeding, mild hematomas, and oozing from puncture sites).

In CHANCE 56% of strokes were intracranial large vessel and 44% other etiologies (majority expected to be small vessel disease) among 1,089 patients with MRA images available, and although there was a larger relative risk reduction in large vessel versus small vessel, the test for interaction was completely consistent with chance ($p = 0.52$).

**POINT**[3]

Major hemorrhage defined as symptomatic intracranial hemorrhage, intraocular bleeding causing vision loss, transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization or prolongation of an existing hospitalization, or death due to hemorrhage.

Minor hemorrhage included asymptomatic intracranial hemorrhage (we obtained data on mild extracranial bleeding by subtracting asymptomatic intracranial hemorrhage (reported in supplementary report) from total minor hemorrhage.

POINT did not report on ischemic stroke subtypes, but it is reasonable to suspect that the majority were probably small vessel (based on exclusion of carotid endarterectomy patients and low NIHSS). From our knowledge of the proportion of patients with aortic arch disease (15%), and other large vessel sources (other than internal carotid artery, ~12%) large vessel etiology (artery to artery) likely make-up an appreciable proportion.

## References


1. Kennedy J, Hill MD, Ryckborst KJ, et al. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol* 2007;6(11):961-9. doi: 10.1016/S1474-4422(07)70250-8
2. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;369(1):11-9. doi: 10.1056/NEJMoa1215340
3. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med* 2018 doi: 10.1056/NEJMoa1800410