**Table S1: Definitions of efficacy and safety outcomes**

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| Outcome Definitions | RE-LY | ROCKET AF | ARISTOTLE |
| Stroke  | Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery and categorized as ischemic, hemorrhagic, or unspecified. Hemorrhagic transformation of ischemic stroke was not considered to be hemorrhagic stroke. Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage. | A sudden focal neurological deficit of presumed cerebrovascular etiology that persisted beyond24 hours and was not due to another identifiable cause. An event matching this definition but lasting less than 2412hours was considered to be a transient ischemic attack. Brain imaging (computed tomography or magnetic resonanceimaging) was recommended for all suspected strokes, and this was performed in 82.1% of patients with strokes. | Stroke was defined as a non-traumatic focal neurologic deficit lasting ≥24 hours.A retinal ischemic event (embolism or thrombosis) was considered a stroke. Acerebral imaging study (computed tomographic scan or magnetic resonanceimaging) was recommended for all suspected strokes.1. Strokes were classified as ischemic, ischemic with hemorrhagictransformation, hemorrhagic, or of uncertain type. Hemorrhagic strokeswere sub-classified as subdural, subarachnoid, or intra-parenchymal.2. A transient ischemic attack (TIA) was defined as a non-traumatic abruptonset of a focal neurologic deficit lasting <24 hours.Stroke and TIA were further sub-classified based on whether there was imagingevidence of a new cerebral infarction that correlated with the clinical presentationof the subject. |
| Systemic embolism  | Systemic embolism was defined as an acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy. | Abrupt vascular insufficiency associated with clinical or radiologicalevidence of arterial occlusion in the absence of another likely mechanism (e.g., atherosclerosis, instrumentation, ortrauma) | The diagnosis of systemic embolism required a clinical history consistent with anacute loss of blood flow to a peripheral artery (or arteries) supported by evidenceof embolism from surgical specimens, autopsy, angiography, vascular imaging,or other objective testing. |
| Major bleeding  | Major bleeding was defined as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. | Clinically overt bleeding associated with any of the following: fataloutcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, orintramuscular with compartment syndrome), fall in hemoglobin concentration >2 g/dL, transfusion of >2 units ofwhole blood or packed red blood cells, or permanent disability | Major bleeding was defined as acute or sub-acute clinically overt bleedingaccompanied by ≥1 of the following:1. a decrease in hemoglobin level of ≥2 g/dL2. a transfusion of ≥2 U of packed red blood cells3. bleeding that was fatal or occurred in the following critical sites: intracranial,intra-spinal, intra-ocular, pericardial, intra-articular, intra-muscularwith compartment syndrome, retroperitoneal. |