Supplemental Appendix

Magnetic Resonance Imaging (MRI) Characteristics and Protocol:

The standard MRI brain protocol performed at Memorial Sloan-Kettering Cancer Center on 1.5 and 3 Tesla scanners (Signa Excite and Signa HDx, GE Healthcare, Milwaukee, Wisconsin) included echo-planar diffusion weighted imaging acquired with a repetition time of 8000 to 10000 milliseconds, an echo time of 60 to100 milliseconds, a field of view of 22 to 24 centimeters squared, a matrix size of 128 by 128, a b-value of 0 and 1000 seconds per millimeter squared, and a number of excitations of one. From 2005 through 2007, slices were acquired at a thickness of 5 millimeters and an interslice gap of 2.5 millimeters, and since 2008 at a thickness of 5 millimeters and no interslice gap. Apparent diffusion coefficient maps were calculated, and all sites of acute ischemia were confirmed as hyperintense on diffusion weighted imaging and hypointense on apparent diffusion coefficient maps by an experienced, board-certified neuroradiologist.

Systematic Methods used to Determine Stroke Mechanisms:

In order to reliably determine stroke mechanisms, study neurologists rigorously reviewed all available patient medical records, including all clinical visits, neuroimaging studies, cardiac evaluations, and laboratory tests, in that specific order. In addition, the reviewers did not rely on clinical reports and closely inspected all neuroimaging studies and electrocardiograms themselves. Furthermore, to ensure that their TOAST (Trial of ORG 10172 in Acute Stroke Treatment Study) mechanistic assessments closely followed established criteria, they performed their assessments with immediate access to the original methodological paper validating the criteria.[1]

Outcome Definitions:

Recurrent thromboembolic event: composite of any recurrent ischemic stroke, transient ischemic attack, myocardial infarction, systemic embolism, deep vein thrombosis including cerebral vein thrombosis, or pulmonary embolism.

Recurrent ischemic stroke: New neurologic deficit(s) with corresponding MRI evidence of acute ischemia in a referable location, and no clinical or radiologic indication of a non-cerebrovascular cause (e.g., metastasis, seizure, migraine, etc.).

Transient Ischemic Attack: Transient neurologic deficit lasting less than 24 hours, attributed to focal brain ischemia without MRI evidence of an acute infarct or clinical evidence for a non-ischemic etiology (e.g., seizure, migraine, encephalopathy, etc.).

Myocardial Infarction: Any combination of two of the following three criteria: chest pain, elevated cardiac enzymes (as per specific laboratory guidelines), or dynamic electrocardiogram changes (e.g. new Q-waves, ST elevations or depressions, or T-wave inversions).

Systemic Embolism: Defined either clinically by the development of typical symptoms of acute limb or mesenteric ischemia (e.g., sudden onset of limb pain, pallor, or pulselessness; or abdominal pain or hematochezia) or by demonstration of vessel occlusion on angiography.

Deep Vein Thrombosis: Thrombosis of an upper or lower extremity, pelvic, or cerebral deep vein diagnosed via Doppler examination, magnetic resonance venography, or spiral computed tomogram (CT).

Pulmonary Embolus: Thrombosis of a pulmonary vein diagnosed by spiral CT of the chest or V/Q scan.

Intracranial Hemorrhage: Extravasation of blood into the brain parenchyma, subarachnoid space, subdural space, or epidural space as demonstrated by neuroimaging, surgery, or autopsy.

Symptomatic Intracranial Hemorrhage: Intracranial bleeding associated with any documentation of clinical deterioration or leading to death.

Major Bleeding: Bleeding associated with death, occurring at a critical site (intracranial, intraocular, intraspinal, retroperitoneal, or pericardial), requiring two or more units of transfused blood, or resulting in a reduction of the hemoglobin level by 2 mg/dl or more.

Methods of Additional Statistical Analyses:

In order to analyze the effect of our primary outcome on survival, we performed Cox proportional hazard regression with recurrent thromboembolism inserted as a time-varying covariate. This time-to-event analysis was performed for the entire cohort and for patients with adenocarcinoma histology only. We also conducted a modified Kaplan-Meier survival analysis, per the methods of Simon and Makuch, to account for time-varying exposures.[2] These time-varying methods of analysis were specifically used to prevent the occurrence of immortal time bias, which often occurs when the relationship between time-varying exposures and clinical outcomes are evaluated with time-fixed methodologies.[3]

Supplemental References:

1. Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.

2. Simon R, Makuch RW. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder versus non-responder bias. Stats Med 1984;3:35-44.

3. Shintani AK, Girard TD, Eden SK, Arbogast PG, Moons KG, Ely EW. Immortal time bias in critical care research: application of time-varying Cox regression for observational cohort studies. Crit Care Med 2009;37:2939-2945.