

Appendix 3: Type of hemorrhagic and thromboembolic events included in each study and the criteria required for each event (part 1 of 5)

| Study | No. of patients | Event characteristics | | | | | | | |
|------------------------|-----------------|---|--|---|--|--|--|-----------|---|
| | | Gastrointestinal | Intracranial | Urogenital | Ocular | Retroperitoneal | Muscular hematoma | Articular | Other hemorrhages |
| Hutten ¹ | 1 303 | Hemoglobin reduction of 2 g/dL or more, transfusion required or discontinuation of anticoagulant required | Confirmed by objective diagnostic tests† | Hemoglobin reduction of 2 g/dL or more, transfusion required or discontinuation of anticoagulant required | | Confirmed by objective diagnostic tests† | | | Hemoglobin reduction of 2 g/dL or more, transfusion required or discontinuation of anticoagulant required |
| Yasaka ² | 203 | Admission to hospital required or transfusion required | Admission to hospital required or transfusion required | | Admission to hospital required or transfusion required | | | | Admission to hospital required or transfusion required |
| EAF ³ | 214 | Admission to hospital and transfusion required, or permanent disability due to hemorrhagic event | Admission to hospital and transfusion required, or permanent disability due to hemorrhagic event | Admission to hospital and transfusion required, or permanent disability due to hemorrhagic event | | | | | Admission to hospital and transfusion required, or permanent disability due to hemorrhagic event |
| Chimowitz ⁴ | 289 | Admission to hospital, transfusion or surgery required | Confirmed by objective diagnostic tests† | Admission to hospital, transfusion or surgery required | Admission to hospital, transfusion or surgery required | | Admission to hospital, transfusion or surgery required | | Admission to hospital, transfusion or surgery required |
| Andersen ^{5*} | 204 | | | | | | | | |
| Torn ⁶ | 356 | Admission to hospital required | Confirmed by objective diagnostic tests† | Admission to hospital required | | | | | Admission to hospital required |
| Cheung ⁷ | 555 | Transfusion required | Transfusion required | | | | | | |
| ESPRIT ⁸ | 536 | | Confirmed by objective diagnostic tests† | | | | | | Admission to hospital required |

Appendix 3: Type of hemorrhagic and thromboembolic events included in each study and the criteria required for each event (part 2 of 5)

| Study | No. of patients | Event characteristics | | | | | | | |
|------------------------------|-----------------|--|--|--|--|--|--|--|--|
| | | | | | | | | | |
| Poli ⁹ | 903 | Surgery or transfusion required or hemoglobin reduction of 2 g/dL or more | Confirmed by objective diagnostic tests† | | Blindness due to hemorrhagic event | Surgery or transfusion required or hemoglobin reduction of 2 g/dL or more | | Surgery or transfusion required or hemoglobin reduction of 2 g/dL or more | Surgery or transfusion required or hemoglobin reduction of 2 g/dL or more |
| Tangelder ¹⁰ | 1 326 | Admission to hospital required | Admission to hospital required | Admission to hospital required | | | | | Admission to hospital required |
| Kearon ¹¹ | 738 | Admission to hospital or transfusion required | | | | Admission to hospital or transfusion required | Admission to hospital or transfusion required | | Admission to hospital or transfusion required |
| Casais ¹² | 811 | Admission to hospital and transfusion required | Admission to hospital and transfusion required | | Blindness due to hemorrhagic event | | Admission to hospital and transfusion required | | Admission to hospital and transfusion required |
| Palareti ¹³ | 2 745 | Surgery or transfusion required, or hemoglobin reduction of 2 g/dL or more | Confirmed by objective diagnostic tests† | Surgery or transfusion required, or hemoglobin reduction of 2 g/dL or more | Blindness due to hemorrhagic event | Surgery or transfusion required, or hemoglobin reduction of 2 g/dL or more | Surgery or transfusion required, or hemoglobin reduction of 2 g/dL or more | Surgery or transfusion required, or hemoglobin reduction of 2 g/dL or more | Surgery or transfusion required, or hemoglobin reduction of 2 g/dL or more |
| Van Walraven ¹⁴ | 10 020 | Admission to hospital required | Admission to hospital required | Admission to hospital required | | Admission to hospital required | | | |
| Azar ¹⁵ | 1 700 | Admission to hospital required | Confirmed by objective diagnostic tests† | | | | Admission to hospital required | | Admission to hospital required |
| Hylek ¹⁶ | 13 559 | | Confirmed by objective diagnostic tests† | | | | | | |
| Oden ¹⁷ | 42 451 | | | | | | | | Fatal events only |
| Thromboembolic events | | Ischemic stroke | Myocardial infarction | Transient ischemic attack | Deep vein thrombosis | Pulmonary embolism | Systemic embolism | Recurrent venous thromboembolism | Thromboses of prosthetic valve |
| Rosove ¹⁸ | 55 | Confirmed by objective diagnostic tests† | Confirmed by objective diagnostic tests† | Confirmed by objective diagnostic tests† | Confirmed by objective diagnostic tests† | Confirmed by objective diagnostic tests† | | | |
| Hutten ¹ | 1 303 | | | | | | | Confirmed by objective diagnostic tests† | |

Appendix 3: Type of hemorrhagic and thromboembolic events included in each study and the criteria required for each event (part 3 of 5)

| Study | No. of patients | Event characteristics | | |
|------------------------|-----------------|--|--|--|
| | | | | |
| Yasaka ² | 203 | NIH stroke scale scores used to assess events | NIH stroke scale scores used to assess events | NIH stroke scale scores used to assess events |
| EAF ³ | 214 | Confirmed by objective diagnostic tests† | History of chest discomfort, specific cardiac enzyme levels more than twice the upper limit of normal or development of Q waves on a standard 12-lead ECG‡ | Confirmed by objective diagnostic tests† |
| Chimowitz ⁴ | 289 | Focal neurologic deficit of sudden onset that lasted at least 24 h and confirmed by objective diagnostic tests | | |
| Andersen ^{5*} | 204 | | | |
| Torn ⁶ | 356 | Confirmed by objective diagnostic tests† | History of chest discomfort, specific cardiac enzyme levels more than twice the upper limit of normal or development of Q waves on a standard 12-lead ECG‡ | Confirmed by objective diagnostic tests† |
| Cheung ⁷ | 555 | Not reported | | Vascular insufficiency of limbs or internal organs |

Appendix 3: Type of hemorrhagic and thromboembolic events included in each study and the criteria required for each event (part 4 of 5)

| Study | No. of patients | Event characteristics | | | | | |
|----------------------------|-----------------|---|--|--------------------------------|--------------------------------|--------------------------------|--|
| | | | | | | | |
| ESPRIT ⁸ | 536 | Focal neurologic deficit of sudden onset that lasted at least 24 h, confirmed by objective diagnostic tests and increase in handicap of at least 1 grade on the modified Rankin scale | History of chest discomfort, specific cardiac enzyme levels more than twice the upper limit of normal or development of Q waves on a standard 12-lead ECG‡ | | | | |
| Poli ⁹ | 903 | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| Tangelder ¹⁰ | 1 326 | Focal neurologic deficit of sudden onset that lasted at least 24 h and increase in handicap of at least 1 grade on the modified Rankin scale | History of chest discomfort, specific cardiac enzyme levels more than twice the upper limit of normal or development of Q waves on a standard 12-lead ECG‡ | | | | |
| Kearon ¹¹ | 738 | | | | | | Confirmed by objective diagnostic tests† |
| Palareti ¹⁹ | 2 745 | Not reported | Not reported | Not reported | Not reported | | Not reported |
| Van Walraven ¹⁴ | 10 020 | Admission to hospital required | Admission to hospital required | Admission to hospital required | Admission to hospital required | Admission to hospital required | |
| Azar ¹⁵ | 1 700 | Confirmed by objective diagnostic tests† | History of chest discomfort, specific cardiac enzyme levels more than twice the upper limit of normal or development of Q waves on a standard 12-lead ECG‡ | | | Not reported | |

Appendix 3: Type of hemorrhagic and thromboembolic events included in each study and the criteria required for each event (part 5 of 5)

| Study | No. of patients | Event characteristics |
|---------------------|-----------------|--|
| Hylek ¹⁶ | 13 559 | Focal neurologic deficit of sudden onset that lasted at least 24 h |

Note: EAFT = European Atrial Fibrillation Trial Study Group, ECG = electrocardiogram, ESPRIT = European and Australian Stroke Prevention in Reversible Ischaemia Trial, NIH = National Institutes of Health.

*Andersen et al. did not report the type of events included or the criteria required for each type of event.

†Diagnostic tests include computed tomography scans, magnetic resonance imaging, angiography, surgery and autopsy.

‡Two of the 3 criteria must be met.

References

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