Vitamin K Antagonists and Risk of Subdural Hematoma
Meta-Analysis of Randomized Clinical Trials

Ben J. Connolly, BSc; Lesly A. Pearce, MS; Robert G. Hart, MD

Background and Purpose—Subdural hematomas are an important bleeding complication of anticoagulation. We quantify the risk of subdural hematoma associated with anticoagulation with vitamin K antagonists (VKAs) compared with other oral antithrombotic therapies.

Methods—Randomized trials were identified from the Cochrane Central Register of Controlled Trials and were included if published since 1980 and compared oral VKAs with antiplatelet therapy or with direct-acting oral anticoagulants. Two reviewers independently extracted data with differences resolved by joint review.

Results—Nineteen randomized trials were included that involved 92,156 patients and 275 subdural hematomas. By meta-analysis, VKAs were associated with a significantly increased risk of subdural hematoma (odds ratios, 3.0; 95% confidence interval, 1.5–6.1) compared with antiplatelet therapy (9 trials, 11,603 participants). The risk of subdural hematoma was also significantly higher with VKAs versus factor Xa inhibitors (meta-analysis odds ratios, 2.9; 95% confidence interval, 2.1–4.1; 5 trials, 49,687 patients) and direct thrombin inhibitors (meta-analysis odds ratios, 1.8; 95% confidence interval, 1.2–2.7; 5 trials, 30,866 patients) versus VKAs. The absolute rate of subdural hematoma among 24,485 patients with atrial fibrillation treated with VKAs pooled from 6 trials testing direct-acting oral anticoagulants was 2.9 (95% confidence interval, 2.5–3.5) per 1000 patient-years.

Conclusions—VKAs use significantly increases the risk of subdural hematoma by ≈3-fold relative to antiplatelet therapy. Direct-acting oral anticoagulants are associated with a significantly reduced risk of subdural hematomas versus VKAs. Based on indirect comparisons to VKAs, the risks of subdural hematoma are similar with antiplatelet monotherapies and factor Xa inhibitors. (Stroke. 2014;45:1672-1678.)

Key Words: anticoagulants ■ aspirin ■ hematoma, subdural ■ intracranial hemorrhages ■ warfarin

Intracranial hemorrhage is the most serious complication of warfarin and other oral vitamin K antagonists (VKAs). About one third of intracranial hemorrhages during VKA therapy are subdural hematomas, collections of blood between the dura mater and the surface of the brain that result from bleeding from the bridging leptomeningeal veins. Subdural hematomas (the other intracranial hemorrhage) have received scant attention relative to the more devastating primary intracerebral hemorrhages, but they have health consequences comparable to ischemic strokes and carry an overall 20% mortality. The risk of subdural hematoma associated with the use of VKAs has not been well defined.

We undertook systematic review and meta-analyses of randomized clinical trials testing VKAs compared with antiplatelet therapy and with direct-acting oral anticoagulants to quantify the risk of subdural hematoma associated with VKA therapy.

Methods

Randomized clinical trials testing oral VKAs were sought by a computerized search of the Cochrane Central Register of Controlled Trials from 1980 to June 2013 (the era of modern neuroimaging required to diagnose subdural hematomas reliably), not restricted by language. In addition, reference lists from systematic reviews of randomized trials of VKAs in patients with atrial fibrillation and VKAs in coronary artery disease were reviewed. We screened the abstracts of 1667 articles and identified 110 articles that seemed relevant for full review (Figure 1). We included all trials reporting randomized comparisons of oral VKAs with antiplatelet monotherapy or with direct-acting oral anticoagulants, that included >1-month treatment, and that reported the occurrence of ≥1 subdural hematoma (trials reporting no subdural hematomas were excluded). Additionally, we contacted the investigators of trials that did not report subdural hematomas if the trials were published after 1998 and either reported ≥5 intracranial hemorrhages, had >1000 participants, or reported ≥20 major bleeds. All subdural hematomas, acute and chronic and traumatic and atraumatic, were included. Trials were excluded if they tested low-dose VKA anticoagulation in which the mean intensity of anticoagulation was not prolonged.
Data Synthesis

Intention-to-treat results were used for the analyses when available (and footnoted when not). Meta-analyses of the trial results are presented as odds ratios (OR) computed assuming a random effects model with the assumption of statistical homogeneity of the treatment effect (across trials) tested using the Q_\text{t} statistic for the relative odds scale. The fixed effects model was chosen if rarity of events, and if the count in ≥1 of the cells for a trial was 0, then 0.5 was added to each of the 4 cells. ORs for individual trials are reported if the total number of subdural hematomas was ≥20. Heterogeneity across trials was also evaluated using the I^2 index (percentage of the total variability in a set of effect sizes because of between-studies variability). Rates of occurrence and confidence intervals (CIs) across trials were computed by dividing the total number of subdural hematomas by the total patient-years of exposure and assuming a Poisson distribution. All CIs and P values are 2-sided; α of 0.05 was accepted as statistically significant. MedCalc for Windows, version 12.7.7 (MedCalc Software, Mariakerke, Belgium) and SPSS, version 20 were the software used.

Results

Nineteen randomized trials involving 92,156 patients were included that compared VKAs with antiplatelet therapy (9 trials, 11,603 participants) or direct-acting oral anticoagulants (10 trials, 80,553 participants) (Table 1). In 11 trials involving 46,764 participants, subdural hematomas were not reported, and unpublished data were obtained from the study investigators. The 9 trials involving patients with atrial fibrillation contributed most patients (70%, n=64,609), with 5 large trials testing direct-acting oral anticoagulants in atrial fibrillation accounting for 66% of patients (n=60,694) (Table 1).

VKA Versus Antiplatelet Therapy

Data regarding subdural hematoma were available from 9 randomized trials (including unpublished data from 6 trials) with 11,603 patients and 34 subdural hematomas (Tables 1 and 2). Trial participants included patients with atrial fibrillation (3 trials), noncardioembolic stroke (4 trials), and heart failure/reduced left ventricular ejection fraction (2 trials). Mean participant age was 65 years (range, 61–82 years), and the mean achieved INRs ranged from 2.1 to 3.2 (Table 2). Antiplatelet therapy was aspirin (dose range, 30–1300 mg/d) except 1 trial each that tested triflusal 600 mg/d and clopidogrel 75 mg/d. Compared with antiplatelet therapy, assignment to VKAs was associated with a significantly increased risk of subdural hematoma (meta-analysis OR, 3.0; 95% CI, 1.5, 6.1; F index, 0%; P=0.8 for heterogeneity). When restricted to the 8 trials in which the mean achieved INR was between 2 and 3, the meta-analysis OR associated with VKA use was 2.8 (95% CI, 1.3–5.8). When restricted to 8 comparisons of VKA with aspirin, the meta-analysis OR was 2.3 (95% CI, 1.1, 5.0).

VKA Versus Oral Direct Factor Xa Inhibitors

Five trials involving 49,687 patients with a mean age of 68 years and 146 subdural hematomas compared warfarin (target INR range, 1.6–3.0) with rivaroxaban, apixaban, or edoxaban in patients with atrial fibrillation (3 trials) or venous thromboembolism (2 trials) (Tables 1 and 3). In 3 of these trials, per-protocol/modified intention-to-treat analyses excluded <1%
Table 1. Randomized Trials Comparing VKA With Antiplatelet Therapy or Direct-Acting Oral Anticoagulants With Accessible Data About Subdural Hematoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Population</th>
<th>Mean Achieved Anticoagulation Intensity (Target Range)/Comparator</th>
<th>Mean Age, y</th>
<th>Male, %</th>
<th>Mean Follow-Up, y</th>
<th>Jadad Score</th>
</tr>
</thead>
</table>
| **VKAs vs antiplatelet therapy**

 Trials reporting subdural hematomas

 SPIRIT11 1316 Noncardioembolic stroke INR, ≈3.2 (3–4.5) ASA, 30 mg/d 63 64 1.2 3

 WASID12 569 Recent brain ischemia due to intracranial stenosis INR, 2.5 (2–3) ASA, 1300 mg/d 64 62 1.8 5

 BAFTA13 973 Atrial fibrillation ≥75 y INR, 2.3 (2–3) ASA, 75 mg/d 82 55 2.7 3

 Trials with unpublished results for subdural hematoma

 SPAF II14 1100 Atrial fibrillation PTR, 1.45 (1.3–1.8) ASA, 325 mg/d 70 70 2.7 3

 WARSS15 2206 Noncardioembolic stroke INR, 2.1 (1.4–2.8) ASA, 325 mg/d 63 60 2.0 5

 NASPEA16 479 Atrial fibrillation INR, 2.5 (2–3) Triflusal, 600 mg/d 70 56 2.6 3

 ESPRIT17 1068 Noncardioembolic stroke INR, 2.6 (2–3) ASA, 30–325 mg/d 62 67 4.6 3

 WATCH18 1587 Heart failure INR, 2.6 (2.5–3) ASA, 162 mg/d Clopidogrel, 75 mg/d 63 85 1.9 3

 WARCEF19 2305 Reduced LVEF INR, 2.5 (2–3.5) ASA, 325 mg/d 61 80 3.5 5

 Pooled 11603 ... ... ... ... 65 69 2.6 3.9*

**VKAs vs direct factor Xa inhibitors**

 Trials reporting subdural hematomas

 ROCKET AF20 14 236† Atrial fibrillation INR, ≈2.5 (2–3) Rivaroxaban, 20 mg/d 73 60 1.9 5

 Trials with unpublished results for subdural hematoma

 J-ROCKET AF21 1274† Atrial fibrillation INR, NR (1.6–3) Rivaroxaban, 15 mg/d 71 81 1.4 4

 EINSTEIN-PE22 4832 Venous thromboembolism INR, NR (2–3) Rivaroxaban, 20 mg/d 58 53 0.6 3

 Hokusai-VTE23 8240† Venous thromboembolism INR, NR (2–3) Edoxaban, 60 mg/d 56 57 0.7 5

 ENGAGE AF24 21 105 Atrial fibrillation INR, NR (2–3) Edoxaban, 60 mg/d, 30 mg/d 72 62 2.8 5

 Pooled 49687 ... ... ... ... 68 60 1.9 4.8*

**VKAs vs direct thrombin inhibitors**

 SPORTIF III25 3407 Atrial fibrillation INR, 2.5 (2–3) Ximelagatran, 36 mg BID 70 69 1.5 3

 SPORTIF V26 3922 Atrial fibrillation INR, 2.4 (2–3) Ximelagatran, 36 mg BID 72 69 1.7 5

(Continued)
of randomized patients and reported only on-therapy data for subdural hematoma. The risk of subdural hematoma was significantly higher (meta-analysis OR, 2.9; 95% CI, 0.2.1, 4.1; I² index, 0%; P=0.6 for heterogeneity) for those assigned VKA versus factor Xa inhibitors.

**Table 2.** Subdural Hematomas in Randomized Trials of VKAs vs Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Mean Achieved INR*</th>
<th>No. of Subdurals/No. of Patients</th>
<th>SDH Rate on VKA (n/1000 Patient-Years)</th>
<th>Odds Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean Age, y</td>
<td>Male, %</td>
<td>Mean Follow-Up, y</td>
<td></td>
</tr>
<tr>
<td>RE-LY27</td>
<td>Atrial fibrillation</td>
<td>INR, 2.4 (2–3)</td>
<td>72</td>
<td>64</td>
<td>2.0</td>
</tr>
<tr>
<td>REMEDY34</td>
<td>Venous thromboembolism</td>
<td>INR, =2.5 (2–3)</td>
<td>55</td>
<td>61</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Trials with unpublished results for subdural hematomas

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Mean Achieved INR*</th>
<th>No. of Subdurals/No. of Patients</th>
<th>SDH Rate on VKA (n/1000 Patient-Years)</th>
<th>Odds Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean Age, y</td>
<td>Male, %</td>
<td>Mean Follow-Up, y</td>
<td></td>
</tr>
<tr>
<td>RE-COVER II29</td>
<td>Acute venous thromboembolism</td>
<td>INR, =2.5 (2–3)</td>
<td>56</td>
<td>62</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dabigatran, 150 mg BID</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pooled 30 866 … … 69 65 1.7 3.6*

ASA indicates acetyl salicylic acid; BAFTA, Birmingham Atrial Fibrillation Treatment of the Aged; ENGAGE AF, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation; ESPRIT, European/Australasian Stroke Prevention in Reversible Ischemia Trial; Hokusai-VTE, Hokusai-Venous Thromboembolism; INR, international normalized ratio; J-ROCKET AF, Japanese-Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; LVEF, left ventricular ejection fraction by echocardiography; NASPEAF, National Study for Prevention of Embolism in Atrial Fibrillation; NR, not reported; PTR, prothrombin time ratio; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SPAF, Stroke Prevention in Atrial Fibrillation; SPIRIT, Stroke Prevention in Reversible Ischemia Trial; SPORTIF, Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation; VKA, vitamin K antagonist; WARCEF, Warfarin vs Aspirin in Reduced Cardiac Ejection Fraction; WARSS, Warfarin-Aspirin Recurrent Stroke Study; WASID, Warfarin-Aspirin Symptomatic Intracranial Disease; and WATCH, Warfarin and Antiplatelet Therapy in Chronic Heart Failure. There is no acronym expansion for REMEDY, EINSTEIN-PE or RE-COVER II. *Weighted according to the number of patients in each trial. †Safety population analysis excluded 28 randomized patients, per-protocol analysis excluded 6 randomized patients, and modified intention-to-treat analysis excluded 54 randomized patients.

**VKA Versus Oral Direct Thrombin Inhibitors**

Five trials (3 atrial fibrillation and 2 venous thromboembolism) involving 30 866 patients with a mean age of 69 years compared warfarin with either ximelagatran or dabigatran and included 95 subdural hematomas (Tables 1 and 3). The risk of subdural
Table 3. Subdural Hematomas in Randomized Trials of VKAs vs Direct-Acting Oral Anticoagulants

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Odds Ratios (95% CI)</th>
<th>No. of Subdurals/No. of Patients</th>
<th>SDH Rate on VKA (n/1000 Patient-Years)</th>
<th>Mean Achieved INR</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKAs vs direct factor Xa inhibitors</td>
<td></td>
<td>VKA</td>
<td>Comparator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCKET AF&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Atrial fibrillation</td>
<td>=2.5</td>
<td>22/7125*</td>
<td>12/7111*</td>
<td>2.2</td>
</tr>
</tbody>
</table>
| J-ROCKET AF<sup>21</sup> | Atrial fibrillation | NR | 2/637* | 1/637* | 2.4 | ...
| EINSTEIN-PE<sup>22†</sup> | Venous thromboembolism | =2.5 | 5/2413 | 1/2419 | 2.8 | ...
| Hokusai-VTE<sup>23</sup> | Venous thromboembolism | =2.5 | 9/4122* | 2/4118* | 3.2 | ...
| ENGAGE AF<sup>24</sup> | Atrial fibrillation | =2.5 | 57/7036 | 15/7035, 30 mg | 3.6 | 3.3 (2.1–5.0) |
|                   |                      |                  |                                      | 20/7034, 60 mg   |            |
| Meta-analysis     | ...                  | ...              | 95/21333‡ | 51/28354 | ... | 2.9 (2.1, 4.1) |
| VKAs vs direct thrombin inhibitors | | VKA | Comparator |
| SPORTIF III<sup>25</sup> | Atrial fibrillation | 2.5 | 4/1703* | 6/1704* | 1.7 | ...
| SPORTIF V<sup>26</sup> | Atrial fibrillation | 2.4 | 7/1962* | 5/1960* | 2.5 | ...
| RE-LY<sup>27</sup> | Atrial fibrillation | 2.4 | 36/6022 | 10/6015, 110 mg | 3.1 | 3.6 (1.8, 7.1) |
| REMEDY<sup>28</sup> | Venous thromboembolism | =2.5 | 1/1426 | 0/1430 | 0.5 | ...
| RE-COVER II<sup>29</sup> | Acute venous thromboembolism | 2.5 | 2/1289 | 0/1279 | 3.1 | ...
| Meta-analysis     | ...                  | ...              | 50/12402‡ | 45/18464 | ... | 1.8 (1.2, 2.7) |

CI indicates confidence interval; ENGAGE AF, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation; Hokusai-VTE, Hokusai-Venous Thromboembolism; INR, international normalized ratio; J-ROCKET AF, Japanese-Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; NR, not reported; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SDH, subdural hematoma; SPORTIF, Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation; and VKA, vitamin K antagonist. There is no acronym expansion for REMEDY, EINSTEIN-PE or RE-COVER II.

*Safety population, per-protocol, or on-treatment analysis.
†Additional unspecified intracranial hemorrhages: 2 among VKA assigned and 1 among rivaroxaban assigned.
‡RE-LY<sup>27</sup> and ENGAGE AF<sup>24</sup> patients assigned warfarin counted once.

The rate of subdural hematoma for 24,485 atrial fibrillation patients (mean age, 72 years) treated with VKAs from 6 trials testing direct-acting oral anticoagulants (Table 3) was 2.9 per 1000 patient-years (95% CI, 2.5, 3.5).

**Discussion**

Subdural hematomas are an important hemorrhagic complication of anticoagulation therapy. They account for 10% of all major hemorrhages and for about one third of intracranial hemorrhages during warfarin anticoagulation of elderly patients with atrial fibrillation (Table II in the online-only Data Supplement). The relative risks of subdural hematoma associated with anticoagulation therapies have not been defined previously. These analyses demonstrate that VKAs increase the risk of subdural hematoma by ≈3-fold compared with antiplatelet therapy (meta-analysis OR, 3.0; 95% CI, 1.5, 6.1) and with factor Xa inhibitors in the dosages tested (meta-analysis OR, 2.9; 95% CI, 2.1, 4.1) (Table 4; Figure 2). Compared with direct thrombin inhibitors, the increased risk with VKAs is smaller (meta-analysis OR=1.8; 95% CI, 1.2, 2.7), albeit with a significant dosage-dependent effect seen with dabigatran (Table I in the online-only Data Supplement). In short, the use of VKAs double or triple the risk for subdural hematoma compared with other antithrombotic therapies.

The achieved mean INRs in the included VKA trials fell into a relatively narrow range (2.1–3.2) that approximates the target therapeutic range for most long-term clinical indications. The antithrombotic effects of aspirin seem to be independent of dosage within the ranges tested (50–1300 mg/d) in
trials included in these analyses. Consequently, the increased relative risk for subdural hematoma with VKA therapy relative to aspirin that emerged from this analysis (OR, 2.3; 95% CI, 1.1, 5.0) is likely to be generalizable to most clinical settings. This relative risk translates into an absolute risk of ≈2 additional subdural hematomas per 1000 elderly atrial fibrillation patients given VKAs per year.

In contrast to aspirin therapy, the intensity of anticoagulation is clearly different for different dosages of individual direct-acting oral anticoagulants (as demonstrated by the different effects of the 2 dosages of dabigatran and edoxaban on ischemic stroke and bleeding in the RE-LY study and Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation [ENGAGE AF] trials) and perhaps between agents with similar anticoagulant mechanism. A major caveat pertaining to this meta-analysis concerns pooling data from trials testing different direct-acting oral anticoagulants to estimate their effect on the occurrence of subdural hematoma relative to VKA. A single estimate for the entire class of factor Xa inhibitors or of direct thrombin inhibitors may well be misleading, and indirect comparison between these classes of selective anticoagulants are likely unreliable. However, a general consistency emerged from the available data that the direct-acting oral anticoagulants in the dosages tested are associated with a reduced risk of subdural hematoma compared with conventional intensities of warfarin anticoagulation (Table 4).

The mechanism(s) for the substantially reduced risks of subdural hematoma associated with the direct-acting oral anticoagulants relative to high-quality warfarin anticoagulation is unclear. Comparing the direct-acting oral anticoagulants with warfarin, intracerebral hemorrhage shows similar relative reductions, but major extracranial bleeding is not reduced (and probably increased). Vascular bed–specific hemostasis seems to differ between oral VKAs and direct-acting oral anticoagulants.

These best available estimates of the relative risks of subdural hematoma are similar when VKAs are compared with platelet therapy (OR, 3.0; 95% CI, 1.5, 6.1) and with factor Xa inhibitors (OR, 2.9; 95% CI, 2.1, 4.1), supporting similar risks of these 2 types of antithrombotic therapies on precipitating subdural hematoma (Table 4). When the trials comparing VKA versus platelet therapy are included in a meta-analysis with the 5 trials comparing VKA versus direct factor Xa inhibitors, there is no suggestion of heterogeneity of treatment effect (meta-analysis OR, 2.9; 95% CI, 2.1, 4.0; F index, 0%; P=0.9 for heterogeneity). However, CIs are relatively wide, the effect of factor Xa inhibitors on subdural hematomas may be dose dependent (Table I in the online-only Data Supplement), and indirect comparisons are problematic, particularly with different patient populations. Only limited data (6 total subdural hematomas from 1 randomized trial) are available from direct randomized comparisons of factor Xa inhibitors with aspirin.

Additional limitations include that subdural hematomas were not a primary or secondary outcome in any of the published trials, necessitating that the numbers of subdural hematomas in the published reports be accepted without details about imaging (eg, acute versus chronic), without distinguishing those associated with trauma from those presumed to be atraumatic, and without description of symptoms prompting their discovery. These caveats apply particularly to the unpublished data. VKA use was reported to be more frequently associated with atraumatic subdural hematomas versus traumatic in a recent surgical series. It is uncertain whether there is an early high-risk period for subdural hematoma after initiation of VKA in VKA-naive patients, similar to that seen with intracerebral hemorrhages. A unique strength of the study is inclusion of unpublished data from 11 trials, comprising 52% of the subdural hematomas analyzed, that were previously inaccessible. Data about the risk of subdural hematoma were available from all large recent randomized trials testing VKAs except for a single trial comparing warfarin with apixaban from which number of subdural hematomas was not available.

Subdural hematomas are an important complication of warfarin anticoagulation of the elderly. Subdural hematomas are well-known to recur (≈20% during short-term follow-up in neurosurgical series). The risks of subdural hematoma associated with direct-acting oral anticoagulants are significantly lower than that for VKAs (odds ratio 0.34 for pooled results of trials comparing factor Xa inhibitors and 0.55 for pooled results of trials comparing direct thrombin inhibitors), offering the opportunity of reducing the morbidity and mortality associated with other subdural hematoma in elderly patients requiring anticoagulation.

Acknowledgments

We gratefully acknowledge the following colleagues for providing unpublished data regarding subdural hematomas from previously reported randomized clinical trials: Dr Francisco Perez-Gomez (Hospital Clinico San Carlos, Madrid, Spain) for National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) data, Dr J.L.P. Thompson, R. Buchsbaum, Dr Shunichi Homma, and Dr J.P. Mohr (Columbia University, New York, NY) for Warfarin-Aspirin Recurrent Stroke Study (WARSS) and Warfarin vs Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) data, Dr Joseph F. Collins (Veterans Administration Medical Center, Perry Point, MD) for the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) data, Dr Ale Algra (University Medical Center Utrecht, Utrecht, The Netherlands) for European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRT) data, Professor Masatsugu Hori (Osaka Medical Center for Cancer and Cardiovascular Research, Osaka, Japan) for Japanese-Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (J-ROCKET) data, Professor Harry Buller (Academic Medical Center, Amsterdam, The Netherlands) for EINSTEIN PE data and Hokusai-Venous Thromboembolism (Hokusai-VTE) study; Dr Sam Schulman (McMaster University, Hamilton, Canada) for RECOVER II, and Dr Robert P. Giugliano (Brigham and Women’s Hospital, Boston, MA) for Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation (ENGAGE AF).
Disclosures
Dr Hart received research support from Bayer Healthcare (rivaroxaban). The other authors report no conflicts.

References
17. ESPRIT Study Group. Medium intensity oral antiocoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT); a randomized controlled trial. Lancet Neurol. 2007;6:115–124.
Vitamin K Antagonists and Risk of Subdural Hematoma: Meta-Analysis of Randomized Clinical Trials

Ben J. Connolly, Lesly A. Pearce and Robert G. Hart

*Stroke*. 2014;45:1672-1678; originally published online May 13, 2014;
doi: 10.1161/STROKEAHA.114.005430

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/6/1672

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/05/13/STROKEAHA.114.005430.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/
**SUPPLEMENTAL MATERIAL**

Supplemental Table I. Effects of high-dose vs. low-dose dabigatran and edoxaban on subdural hematoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Agent / dosages</th>
<th># subdurals / # patients</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY (2009)</td>
<td>atrial fibrillation</td>
<td>dabigatran 110 vs. 150 mg twice daily</td>
<td>10 / 6015</td>
<td>24 / 6076</td>
</tr>
<tr>
<td>ENGAGE AF (2013)</td>
<td>atrial fibrillation</td>
<td>edoxaban 30 vs. 60 mg daily^</td>
<td>15 / 7034</td>
<td>20 / 7035</td>
</tr>
</tbody>
</table>

^Dosage halved for patients with estimated creatinine clearance 30-50 mL/min, body weight of 60kg or less, or concomitant use of potent P-glycoprotein inhibitors, affecting 25% of participants at randomization.

Supplemental Table II. Fraction of major hemorrhages due to subdural hematoma in recent (published between 2003 and 2013) studies of vitamin K antagonists in atrial fibrillation patients.^

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of anticoagulated patients (mean age)</th>
<th>Number (annualized rate) of major hemorrhages^</th>
<th>Fraction due to intracranial hemorrhage (n)</th>
<th>Fraction due to subdural hemorrhage (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPORTIF III (2003)(3)</td>
<td>1703 (70 yrs)</td>
<td>50 (2.2%/yr)</td>
<td>22% (11)</td>
<td>8% (4)</td>
</tr>
<tr>
<td>SPORTIF V (2005)(4)</td>
<td>1962 (72 yrs)</td>
<td>93 (3.4%/yr)</td>
<td>10% (9)</td>
<td>8% (7)</td>
</tr>
<tr>
<td>BAFTA (2007)(5)</td>
<td>488 (82 yrs)</td>
<td>25 (1.9%/yr)</td>
<td>32% (8)</td>
<td>8% (2)</td>
</tr>
<tr>
<td>ATRIA (2007)(6)</td>
<td>9217 (NR)</td>
<td>170 (1.1%/yr)</td>
<td>42% (72)</td>
<td>9% (15)</td>
</tr>
<tr>
<td>RE-LY (2009)(1)</td>
<td>6022 (72 yrs)</td>
<td>397 (3.4%/yr)</td>
<td>26% (87)</td>
<td>11% (36)</td>
</tr>
<tr>
<td>ROCKET AF (2011)(7)</td>
<td>7125# (73 yrs)</td>
<td>386 (3.4%/yr)</td>
<td>22% (84)</td>
<td>6% (22)</td>
</tr>
<tr>
<td>J-ROCKET (2011)(8)</td>
<td>639 (71 yrs)</td>
<td>30 (3.6%/yr)</td>
<td>33% (10)</td>
<td>7% (2)</td>
</tr>
<tr>
<td>ARISTOTLE (2011)(9)</td>
<td>9081 (70 yrs)</td>
<td>462 (3.1%/yr)</td>
<td>26% (122)</td>
<td>10% (44)*</td>
</tr>
<tr>
<td>ENGAGE AF (2013)(2)</td>
<td>7036 (72 yrs)</td>
<td>524 (3.4%/yr)</td>
<td>25% (132)</td>
<td>11% (57)</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td>2137</td>
<td>25% (535)</td>
<td>9% (189)</td>
</tr>
</tbody>
</table>

NR = not reported; yrs = years.
^ Studies with target INR range of 2-3. Criteria for major hemorrhage are that used in the study and vary, but all include intracranial bleeding and subdural hematoma.
+“Safety population”.
*Number of subdural hematomas estimated by subtracting intracerebral hemorrhages from total intracranial hemorrhages.(8)

Supplemental References:


