Risk of Stroke or Systemic Embolism in Atrial Fibrillation Patients Treated With Warfarin

A Systematic Review and Meta-analysis

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a lifetime risk for development of 1 in 4 when ≥40 years of age.1 The presence of this arrhythmia is an independent risk factor for stroke/thromboembolism and death,2,3 with an estimated 5-fold higher risk.4 The value of oral anticoagulation (whether as well-controlled adjusted dose warfarin, or one of the novel anticoagulants) in stroke prevention is well established and recommended in guidelines.5,6 Novel, or new, oral anticoagulants (OACs) may be preferred on the basis of clinical trial data, but clinical experience with these agents is still limited, and further information on their effect in clinical practice is needed, again as emphasized by recent guidelines.7 Furthermore, there remain concerns of the effect of the new OAC drugs in several patient groups, such as the very elderly patients with multiple comorbidities, polypharmacy, and compliance issues, as well as concerns of their use in patients with renal impairment, who are excluded from the trials.8 As long as these uncertainties exist, the vitamin K antagonists (VKA; eg, warfarin) will remain the first choice OAC drug for many physicians, especially primary care physicians, where many of these AF patients are treated.

Although OACs are highly effective in reducing the risk of stroke and mortality in AF, some patients still sustain stroke despite being on an OAC. In the original, now historical, trials of stroke prevention, the efficacy of warfarin in reducing stroke (by 64%) and mortality (by 26%) compared with placebo/control may be underestimated because many strokes in the warfarin arm occurred when patients were not actually taking warfarin or were subtherapeutic.9 Although the importance of good international normalized ratio control is emphasized (as reflected by time in therapeutic range), it would be important to appreciate the risk factors that contribute to stroke risk in AF, although patients are taking OACs. Understanding these risk factors could help re-emphasize the clinical practice shift,

Background and Purpose—Although oral anticoagulants (OACs) are highly effective in reducing stroke risk in atrial fibrillation, some patients still sustain stroke despite being on an OAC. Our aim was to identify the risk factors that contribute to stroke risk in atrial fibrillation, although patients were taking OACs in a clinical trial setting.

Methods—We identified contemporary clinical trials that investigated OACs in patients with atrial fibrillation. Event rates per year from each study and pooled event rates and relative risks, all with a 95% confidence interval, were calculated. Statistical heterogeneity was assessed using the I^2 test.

Results—Six trials were included in the meta-analysis, with a total of 58883 patients randomized. Characteristics associated with a higher relative risk of stroke while on an OAC included age ≥75 years (relative risk, 1.46 [95% confidence interval, 1.25–1.69]), female sex (1.30 [1.15–1.49]), previous stroke/transient ischemic attack (1.85 [1.32–2.60]), vitamin K-antagonist naive status (for vitamin K antagonist experienced, 0.85 [0.74–0.97]), moderate and severe renal impairment (1.54 [1.30–1.81] and 2.22 [1.85–2.66], respectively, compared with normal renal function), previous aspirin use (1.19 [1.04–1.37]), Asian race (1.70 [1.42–2.03]), and a CHADS2 score of ≥3 (1.64 [1.18–2.27]).

Conclusions—Stroke rates are higher on OACs with some patient clinical characteristics, that is, older age, female sex, previous stroke/transient ischemic attack, vitamin K-antagonist naive status, renal impairment, previous aspirin use, and higher CHADS2 score. The identified risk factors for stroke while on an OAC could potentially be used to consider a risk assessment tool to flag up high-risk patients while on an OAC (in this case, warfarin). Whether these risk factors apply to novel OACs is uncertain. (Stroke. 2013;44:00-00.)

Key Words: atrial fibrillation ■ oral anticoagulation ■ stroke ■ warfarin
which has been recommended to focus on better identification of truly low-risk patients with AF.\textsuperscript{5,9} Strokes can effectively be reduced by OAC, especially with novel OACs that offer some efficacy and safety benefits compared with warfarin.\textsuperscript{10}

Previous meta-analyses investigating the effect of warfarin in AF patients have looked at the effect in large heterogeneous groups of patients, with a wide spectrum of risk, as studied in their respective trials.\textsuperscript{7} A recent meta-analysis of 8 randomized controlled trials (RCTs), investigating the safety and efficacy outcomes in AF patients treated with warfarin for stroke prevention, found that current use of warfarin was associated with a low rate of residual stroke or systemic embolism estimated to be 1.66\% per year\textsuperscript{11}; however, not all subgroups of patients at risk despite OACs were studied. Also, their focus on older trials (ie, before 2000) compared with more contemporary trials (in the past decade) may be confounded by different standards of clinical care, including optimization of cardiovascular risk factors.

To address these concerns, we performed a systematic review of the clinical trial literature to find contemporary randomized trials that investigated antithrombotic therapy in patients with AF. We then performed a meta-analysis of the recent RCTs (published after 2002), with particular focus on the warfarin arm of each trial and investigated whether certain subgroups remained at high risk of stroke despite OAC treatment. Our objective was to identify the risk factors that still contributed to stroke/thromboembolic risk in AF, although the patients were taking OACs.

**Methods**

We performed a systematic computerized literature review of clinicaltrials.gov and the major databases (including Medline, Excerpta Medica Database [EMBASE], Cochrane, Cumulative Index to Nursing and Allied Health Literature [CINAHL], etc) to identify RCTs reporting the safety and efficacy of warfarin therapy in non-valvular AF patients. MeSH words and keywords, such as warfarin, AF, VKAs, and RCTs, were coupled with words like stroke, systemic embolism, cerebrovascular accident, and transient ischemic attack.

Trials were included if they were in English and published during the past 10 years (2002–2012). The trials had to be phase III trials investigating warfarin as antithrombotic therapy in AF patients with the composite end point of stroke (ischemic or hemorrhagic) or systemic embolism. The studies had to include ≥400 patients to enable accurate assessment of event rates. Finally, the studies had to be fully published and include subgroup analyses from the warfarin arm of the study for the composite end point of stroke or systemic embolism.

**Data Extraction**

All the titles, their abstracts, and the full-text articles for potentially relevant studies selected, using the search strategy, were retrieved. The full-text articles were subsequently reviewed with a primary focus on subgroup analyses, inclusion criteria, study outcomes, and methodological quality. The data for each included study were extracted. In the trials in which only a total number of patients were given, it was assumed that half were treated with warfarin and half with the comparator. In studies comparing 3 regimens, it was assumed that one third were treated with warfarin. In the analyses in which a number of events were given in percentage instead of rates, it was assumed that the patients from each subgroup were followed up in what was given as the mean follow-up time. If no mean follow-up time was given, median follow-up time was used instead. The extracted data were reviewed for accuracy and validity by 2 researchers (I.E.A., T.F.O.) before being entered into statistical software for analyses.

**Statistical Analyses**

Results are given as events per 100 person years with a 95\% confidence interval (CI). Pooled relative risks (RRs) are graphically presented in forest plots. Assessment of heterogeneity was achieved by comparing the inclusion and exclusion criteria and the minor differences in the design and conduct of the clinical trials. Between-study heterogeneity was assessed using the \( I^2 \) test statistic, where \( I^2 > 50\% \) with \( P < 0.05 \) implies significant heterogeneity. Fixed effect meta-analysis was used to calculate the pooled estimates if the \( I^2 \) test statistic did not imply statistically significant heterogeneity, otherwise the random-effect meta-analysis was used. Pooled RR estimates were only derived using studies where estimates for all strata in a subgroup were available.

For each study, exact 95\% Poisson CIs were calculated for the respective outcome. A \( P < 0.05 \) was considered statistically significant. Pooled estimates for the event rates and RRs were calculated using the meta function in STATA. STATA version 11.2 (Stata Corporation, College Station, TX) was used for the statistical analyses and generation of graphics.

**Results**

Our search identified 162 studies, of which 6 RCTs were finally included for this analysis (Figure 1). Characteristics of the 6 included trials are shown in Table 1. The majority of the trials studied AF patients with ≥1 stroke risk factors, with the exception of Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), which studied a higher risk population. All trials achieved an average time in therapeutic range of >62\%, but with the ROCKET-AF trial being the exception (55\%).

The studies finally included in our analysis were as follows: Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF III)\textsuperscript{12} and (SPORTIF V),\textsuperscript{13} Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA),\textsuperscript{14} Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY),\textsuperscript{15} ROCKET-AF,\textsuperscript{16} and finally Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE).\textsuperscript{17} Studies excluded from the meta-analysis after full-text review are summarized in Table I in the online-only Data Supplement.

Table 2 summarizes the RRs and event rates per 100 person-years (95\% CI) of stroke or systemic embolism in the warfarin arm across trials stratified by subgroups. The overall rate of stroke or systemic embolism during VKA was low. Characteristics associated with a higher RR of stroke while on OACs included age ≥75 years (RR, 1.46 [95\% CI, 1.25–1.69]), female sex (1.30 [1.15–1.49]), previous stroke/transient ischemic attack (1.85 [1.32–2.60]), vitamin K-antagonist naïve status (for VKA experienced, 0.85 [0.74–0.97]), moderate and severe renal impairment as reflected by creatinine clearance of 50 to 80 mL/min and <50 mL/min, respectively (1.54 [1.30–1.81] and 2.22 [1.85–2.66], respectively, compared with normal renal function), previous aspirin use (1.19 [1.04–1.37]), and a CHADS\textsubscript{2} (congestive heart failure, hypertension, age, diabetes mellitus, and previous stroke) score of ≥3 (1.64 [1.18–2.27]).

When stratified by race, stroke rates in America and Europe on OACs were similar, but higher stroke rates in Asia were evident (1.70 [1.42–2.03]). Heart failure, hypertension, diabetes mellitus, and proton pump inhibitor use did not influence stroke rates on OACs. The RRs (95\% CI) that reached statistical significance (except moderate renal impairment) are illustrated in Figure 2.

Event rates in various subgroups while on OACs varied between 1.1\% per year (normal renal function) and 2.74\%
per year (previous stroke/transient ischemic attack), although these rates are univariate comparisons with no adjustments for additional comorbidities in various subgroups. As expected, absolute event rates in the ROCKET-AF trial were generally higher than other trials (even when subdivided by subgroups), given the higher risk study population in that trial. For a histogram illustrating the event rates see Figure I in the online-only Data Supplement.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPORTIF III</td>
<td>AF with age ≥75 yr or hypertension or LV dysfunction or previous stroke/TIA/systemic embolism.</td>
<td>Heart-valve disorder, transient AF, recent stroke/TIA, increased risk of bleeding, endocarditis, atrial myxoma/LV thrombus, recent admission for CAD, chronic OAC treatment, planned cardioversion/surgery, treatment with fibrinolytic agent or NSAID before randomization, CrCl &lt;30/min, active liver disease, pregnancy, anemia, drug/alcohol abuse.</td>
<td>Composite of stroke (ischemic or hemorrhagic) or systemic embolism.</td>
</tr>
<tr>
<td>SPORTIF V</td>
<td>(As above)</td>
<td>(As above)</td>
<td>(As above)</td>
</tr>
<tr>
<td>BAFTA</td>
<td>AF or atrial flutter with age ≥75 yr</td>
<td>Rheumatic heart disease, intracranial hemorrhage, esophageal varices, allergy to used drugs, terminal illness, recent surgery, peptic ulcer or major hemorrhage, BP &gt;180/110 mm Hg, contraindication to warfarin use.</td>
<td>Composite of stroke (ischemic or hemorrhagic), intracranial hemorrhage or arterial embolism.</td>
</tr>
<tr>
<td>RE-LY</td>
<td>AF with age ≥75 yr and previous stroke/TIA/LVEF &lt;40% or NYHA class II or higher symptoms, AF with age &gt;65 yr with DM or hypertension or CAD.</td>
<td>Severe heart-valve disorder, recent stroke, increased risk of hemorrhage, CrCl &lt;30/min, active liver disease, pregnancy.</td>
<td>Composite of stroke (ischemic or hemorrhagic or systemic embolism).</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>AF with previous stroke/TIA/systemic embolism.</td>
<td>Severe heart-valve disorder, planned cardioversion or surgery, transient AF, atrial myxoma/LV thrombus, endocarditis, increased risk of bleeding, internal bleeding, hypertension ≥180/100 mm Hg, low-platelet count, recent stroke/TIA, required anticoagulation, treatment with fibrinolytic agents or cytoP450 inducer before randomization, NSAID treatment, anemia, pregnancy, contraindication to warfarin, HIV infection, CrCl &lt;30/min, liver disease, drug/alcohol abuse.</td>
<td>Composite of stroke (ischemic or hemorrhagic) or systemic embolism.</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>AF or atrial flutter with age ≥75 yr or previous stroke/TIA/systemic embolism.</td>
<td>Transient AF, mitral stenosis, required anticoagulation, recent stroke, need for aspirin/ clopidogrel, CrCl &lt;25/min.</td>
<td>Composite of stroke (ischemic or hemorrhagic) or systemic embolism.</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BAFTA, Birmingham Atrial Fibrillation Treatment of the Aged; BP, blood pressure; CAD, coronary artery disease; CHADS2, Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke or TIA; CrCl, creatinine clearance; DM, diabetes mellitus; INR, international normalized ratio; LV, left ventricle; LVEF, left-ventricular ejection fraction; NSAID, nonsteroidal anti-inflammatory drug; NYHA, New York Heart Association; RE-LY, Randomized Evaluation of Long-term Anticoagulant Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SPORTIF, Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation; and TIA, transient ischemic attack.
In this systematic review and meta-analysis of contemporary clinical trials, we have shown that stroke rates are higher while on OACs with some important patient characteristics, that is, older age, female sex, previous stroke/transient ischemic attack, vitamin K-antagonist naive status, renal impairment, previous aspirin use, and higher CHADS2 score. The identified risk factors for stroke while on OAC could potentially be used...
to develop a risk assessment tool to flag up high-risk patients while on an OAC (in this case, warfarin). Our analysis also provides estimates of the absolute stroke rates during warfarin anticoagulation in the key subgroups; and, for example, even among the highest risk subgroup (previous stroke), the absolute stroke rate is only ≈2.5% per year.

It is known that age is a risk factor for stroke with a lifetime probability of suffering a stroke increasing steadily with age. Figure 2. Forest plots demonstrating pooled relative risks (RRs; 95% confidence interval [CI]) of subgroups. A, Age ≥75 years. B, Female sex. C, Previous stroke/transient ischemic attack, yes. D, Previous vitamin K-antagonist use, yes. Forest plots demonstrating pooled RRs (95% CI) of 8 subgroups. E, Creatinine clearance <50mL/min. F, Previous acetylsalicylic acid use, yes. G, CHADS₂ (Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke or transient ischemic attack) score ≥3. H, Race, Asian. Diamonds indicate the overall summary estimate for the analysis (width of the diamond represents 95% CI). ARISTOTLE indicates Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BAFTA, Birmingham Atrial Fibrillation Treatment of the Aged; RE-LY, Randomized Evaluation of Long-term Anticoagulant Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; and SPORTIF, Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation.
However, the effect of OACs in patients with both these conditions is sparsely investigated. Olesen et al. recently showed that warfarin treatment was associated with a lower risk of stroke or systemic thromboembolism among AF patients with chronic kidney disease. The same conclusion was made by Hart et al. using patients with stage 3 chronic kidney disease participating in the Stroke Prevention in Atrial Fibrillation (SPAF) 3 trial. In the present study, both moderate and severe renal impairment was associated with significantly higher risks of stroke and systemic embolism for patients on OACs compared with patients with normal renal function. However, current stroke risk stratification schemes for AF patients are based on trials that exclude AF patients with severe renal impairment. Large RCTs that assess the real risk/benefit of full-intensity anticoagulation in AF patients with renal impairment are clearly needed.

We found that previous aspirin use is associated with higher RR of stroke or systemic embolism. The indication for the patients to take aspirin is not known, and therefore we cannot (at least based on these results) determine whether it is the aspirin use itself that causes the higher risk or if it is the fact that aspirin use may reflect other comorbidities, such as vascular disease, which is not recorded nor defined in many trials. However, it does not change the fact that previous aspirin use is associated with a higher risk of adverse events.

Many of the data on the clinical epidemiology of AF have been derived from published studies on predominantly white populations in North America or Europe. A few studies have found a lower prevalence of AF among Indo-Asians and a lower incidence of AF in black compared with white populations. These findings are reflected in the general perception that Asians have lower stroke rates than whites. However, a recent review of 38 articles published outside North America or Europe concluded that AF is very much a global issue with a prevalence of AF ranging from 2.8% to 14% in the included hospital-based studies. In our analysis, we show that stroke rates on OACs are evidently higher among Asian subjects. Clearly, high-quality epidemiological studies are required to improve understanding of the worldwide burden of AF and stroke in AF.

These identified risk factors for stroke while on OACs may be used to potentially consider the development of a risk assessment tool to identify high-risk patients while on an OAC (in this case, warfarin), and further study with patient-level data would help. The risk factors identified conform closely to the CHADS2/CHA2DS2-VASc scores, and thus, most of these individuals would be recommended anticoagulation. Although the risk scores may be useful, we need to first show which factors are associated with stroke even during warfarin therapy, as shown in the present analysis. The potential to flag up high-risk patients on OACs could involve improving the time in therapeutic (while on warfarin) or even the use of more efficacious novel OAC drugs.

Because alternatives to warfarin are available (dabigatran, rivaroxaban, apixaban), it would be relevant to identify warfarin-treated patients who may still be high risk and would benefit from different treatment strategies (both improved time in therapeutic range or other agents). Importantly, whether using such treatment strategies would actually
improve the prognosis for these patients cannot be answered based on this analysis. The options of improved time in therapeutic range novel OACs, and more time with their general practitioner, for example, are possibilities; such a package of care intervention in high-risk subjects despite warfarin use would need to be tested in a prospective study.

Limitations
This meta-analysis addresses the primary end point of the 6 included trials. Given the data available on subgroups, some assumptions regarding exact number treated and follow-up time had to be made. Indeed, deviations from similarity are potentially confounding when compared in a meta-analysis. However, the end point was identical in all trials, except in BAFTA, where the end point besides disabling stroke and arterial embolism also included other intracranial hemorrhage, verified by brain imaging.

The strokes actually prevented by warfarin are likely to be mainly thromboembolic in nature and not hemorrhagic, and we have no information on the specific proportion of thromboembolic versus hemorrhagic strokes in the combined end point. Hence, our identified high-risk patients on warfarin may merely be composed of people at high risk for hemorrhagic strokes that are not prevented by warfarin.

In this analysis, we cannot account for time in therapeutic range variation within different subgroups, which would have an important bearing on event rates. In their respective trials, overall time spent in the therapeutic range varied from 55% to 68%. Indeed, predictors of stroke during warfarin anticoagulation could hypothetically be mainly predictors of anticoagulation control, but this possibility cannot be answered by this analysis because we did not have access to mean international normalized ratio values within subgroups. It is likely that higher rates of stroke among warfarin-treated patients are also reflective of poor international normalized ratio control, and this study could then help identify those AF patients who are difficult to keep within target international normalized ratio range and who may be targeted for OAC with one of the novel OACs. Importantly, this study does not provide evidence that these novel OACs will prove more effective among the specific high-risk subgroups.

Furthermore, differences in inclusion and exclusion criteria, patient population, and data collection methods may result in residual confounding and persisting heterogeneity. Indeed, the statistical technique somewhat assumes that patients entered in the trials were fairly comparable. Because the studies had broadly similar inclusion and exclusion criteria, the assumption may be reasonable. The aim of our study was to focus on VKA-treated patients, and further analyses would need to assess whether our observations may be extrapolated to the novel OACs.

Conclusion
We have shown that stroke rates are higher on OACs with some patient characteristics. The identified risk factors for stroke while on OACs could potentially be used to consider a risk assessment tool to flag up high-risk patients while on an OAC (in this case, warfarin). Whether these factors apply to the novel OACs is uncertain.

Acknowledgments
Dr Lip provided the idea for the article and contributed to the interpretation and drafting; I.E. Albertsen and T.F. Overvad helped in literature search, drafting, and revisions; Drs Rasmussen and Larsen contributed to article drafting and revisions; and Dr Graunegaard contributed to statistics.

Disclosures
Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim, and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis. Drs Larsen and Rasmussen have served as speakers for Bayer, BMS/Pfizer, and Boehringer Ingelheim. The other authors have no conflicts to report.

References


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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/03/12/STROKEAHA.113.000883.DC1

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Web-only Table w1: Full-text articles assessed for eligibility not included in the meta-analysis

| “Safety and efficacy of the oral direct factor Xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation”¹ |
| “Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment”² |
| “Warfarin in atrial fibrillation patients with moderate chronic kidney disease”³ |
| “Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation”⁴ |
| “Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial”⁵ |
| “Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with non-valvular atrial fibrillation (PETRO Study)”⁶ |
| “Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial”⁷ |

Web-only references


Web-only Figure w1: Pooled event rates stratified by sub-groups

Event rates per 100 person years

Sub-groups
- Creatinine clearance (CrCl) m/min
  - <80
  - 80-100
  - >100
- Heart failure, Yes/No
- Hypertension, Yes/No
- Diabetes, Yes/No
- Previous ASA use, Yes/No
- Previous PPI use, Yes/No
- Race, America/Asian
- Age (years) <75/75
- Female/Male
- Previous stroke/TIA, Yes/No
- Previous VKA use, Yes/No
- CHADS2 score, 0-2

Figure shown with upper half of the 95% confidence interval

Abbreviations: CrCl: creatinine clearance, ASA: Acetylsalicylic Acid, PPI: Proton Pump Inhibitor