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# Journal Pre-proof



Apixaban versus Aspirin According to CHA<sub>2</sub>DS<sub>2</sub>-VASc Score in Subclinical Atrial Fibrillation: Insights from ARTESiA

Renato D. Lopes, MD, PhD, Christopher B. Granger, MD, Daniel M. Wojdyla, MS, William F. McIntyre, MD, PhD, Marco Alings, MD, Thenmozhi Mani, PhD, Chinthanie Ramasundarahettige, MSc, Lena Rivard, MD, MSc, Dan Atar, MD, David H. Birnie, MD, Giuseppe Boriani, MD, PhD, Guy Amit, MD, MPH, Peter Leong-Sit, MD, MSc, Claus Rinne, MD, Gabor Z. Duray, MD, PhD, Michael R. Gold, MD, PhD, Stefan H. Hohnloser, MD, Valentina Kutiyifa, MD, PhD, Juan Benezet-Mazuecos, MD, PhD, Jens Cosedis Nielsen, DMSc, PhD, Christian Sticherling, MD, MHBA, Alexander P. Benz, MD, MSc, Cecilia Linde, MD, PhD, Joseph Kautzner, MD, PhD, Philippe Mabo, MD, Georges H. Mairesse, MD, Stuart J. Connolly, MD, Jeff S. Healey, MD

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## Apixaban versus Aspirin According to CHA<sub>2</sub>DS<sub>2</sub>-VASc Score in Subclinical Atrial Fibrillation: Insights from ARTESiA

**Brief Title:** Apixaban versus Aspirin by CHA<sub>2</sub>DS<sub>2</sub>-VASc in SCAF

Renato D. Lopes, MD, PhD,<sup>a</sup> Christopher B. Granger, MD,<sup>a</sup> Daniel M. Wojdyla, MS,<sup>a</sup> William F. McIntyre, MD, PhD,<sup>b</sup> Marco Alings, MD,<sup>c</sup> Thenmozhi Mani, PhD,<sup>b</sup> Chinthanie Ramasundarahettige, MSc,<sup>b</sup> Lena Rivard, MD, MSc,<sup>d</sup> Dan Atar, MD,<sup>e</sup> David H. Birnie, MD,<sup>f</sup> Giuseppe Boriani, MD, PhD,<sup>g</sup> Guy Amit, MD, MPH,<sup>h</sup> Peter Leong-Sit, MD, MSc,<sup>i</sup> Claus Rinne, MD,<sup>j</sup> Gabor Z. Duray, MD, PhD,<sup>k</sup> Michael R. Gold, MD, PhD,<sup>l</sup> Stefan H. Hohnloser, MD,<sup>m</sup> Valentina Kutuyifa, MD, PhD,<sup>n</sup> Juan Benezet-Mazuecos, MD, PhD,<sup>o</sup> Jens Cosedis Nielsen, DMSc, PhD,<sup>p</sup> Christian Sticherling, MD, MHBA,<sup>q</sup> Alexander P. Benz, MD, MSc,<sup>b,r</sup> Cecilia Linde, MD, PhD,<sup>s</sup> Joseph Kautzner, MD, PhD,<sup>t</sup> Philippe Mabo, MD,<sup>u</sup> Georges H. Mairesse, MD,<sup>v</sup> Stuart J. Connolly, MD,<sup>b</sup> Jeff S. Healey, MD<sup>b</sup>

<sup>a</sup>Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC;

<sup>b</sup>Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada;

<sup>c</sup>Amphia Ziekenhuis, Breda, Netherlands; <sup>d</sup>Department of Cardiology, Montreal Heart Institute, Université de Montréal, Canada; <sup>e</sup>Division of Cardiology, Oslo University Hospital Ulleval, and Institute of Clinical Medicine, University of Oslo, Norway; <sup>f</sup>University of Ottawa Heart Institute, Ottawa, ON, Canada; <sup>g</sup>Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy;

<sup>h</sup>McMaster University-Hamilton Health Sciences, Hamilton, Ontario, Canada; <sup>i</sup>Department of Cardiology, Western University, London, ON, Canada; <sup>j</sup>St Mary's Regional Cardiac Center,

Kitchener, ON, Canada; <sup>k</sup>Department of Cardiology, Central Hospital of Northern Pest-Military Hospital, and Heart and Vascular Center, Semmelweis University, Budapest, Hungary;

<sup>l</sup>Department of Medicine, Medical University of South Carolina, Charleston, SC; <sup>m</sup>J.W.Goethe University, Frankfurt, Germany; <sup>n</sup>University of Rochester, School of Medicine and Dentistry, Rochester, NY; <sup>o</sup>Cardiology Department, Hospital Universitario La Luz, Madrid, Spain;

<sup>p</sup>Department of Clinical Medicine, Aarhus University, and Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; <sup>q</sup>Department of Cardiology, University Hospital Basel, University of Basel, Switzerland; <sup>r</sup>Department of Cardiology, University Medical Center Mainz, Johannes Gutenberg-University, Mainz, Germany; <sup>s</sup>Karolinska Institutet, Stockholm, Sweden; <sup>t</sup>Institute for Clinical and Experimental Medicine, Prague, Czech Republic; <sup>u</sup>Cardiology and Vascular Disease Division, Rennes University Health Centre, Rennes, France; <sup>v</sup>Cliniques du Sud Luxembourg, Department of Cardiology, Arlon, Belgium.

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**Address for correspondence:** Renato D. Lopes, MD, MHS, Ph.D, Duke Clinical Research Institute, 200 Morris Street, Durham, NC 27701. Phone: (919) 668-8241; Fax: (919) 668-7056. E-mail [renato.lopes@dm.duke.edu](mailto:renato.lopes@dm.duke.edu).

**Tweet:** Subclinical atrial fibrillation (SCAF) is common in patients with implanted devices. Identifying patients who benefit the most from oral anticoagulation is needed in clinical practice. In this current subgroup analysis from the ARTESiA trial, we showed that CHA<sub>2</sub>DS<sub>2</sub>-VASc score, the current standard for guiding the treatment of clinical AF, helps in guiding oral anticoagulation for patients with SCAF.

#DCRI; #PHRI; #RenatoLopes

**Abstract**

**Background:** ARTESiA demonstrated that apixaban, compared with aspirin, significantly reduced stroke and systemic embolism (SE) but increased major bleeding in patients with subclinical atrial fibrillation (SCAF).

**Objectives:** To help inform decision making, we evaluated the efficacy and safety of apixaban according to baseline CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

**Methods:** We performed a subgroup analysis according to baseline CHA<sub>2</sub>DS<sub>2</sub>-VASc score and assessed both the relative and absolute differences in stroke/SE and major bleeding.

**Results:** Baseline CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were <4 in 1578 (39.4%) patients, 4 in 1349 (33.6%), and >4 in 1085 (27.0%). For patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc >4, the rate of stroke was 0.98%/year with apixaban and 2.25%/year with aspirin; compared with aspirin, apixaban prevented 1.28 (0.43 to 2.12) strokes/SE per 100 patient-years and caused 0.68 (-0.23 to 1.57) major bleeds. For CHA<sub>2</sub>DS<sub>2</sub>-VASc <4, the stroke/SE rate was 0.85%/year with apixaban and 0.97%/year with aspirin. Apixaban prevented 0.12 (-0.38 to 0.62) strokes/SE per 100 patient-years and caused 0.33 (-0.27 to 0.92) major bleeds. For patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc =4, apixaban prevented 0.32 (-0.16 to 0.79) strokes/SE per 100 patient-years and caused 0.28 (-0.30 to 0.86) major bleeds.

**Conclusion:** One in 4 patients in ARTESiA with SCAF had a CHA<sub>2</sub>DS<sub>2</sub>-VASc score >4 and a stroke/SE risk of 2.2% per year. For these patients, the benefits of treatment with apixaban in preventing stroke/SE are greater than the risks. The opposite is true for patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score <4. A substantial intermediate group (CHA<sub>2</sub>DS<sub>2</sub>-VASc =4) exists in which patient preferences will inform treatment decisions.



**Condensed abstract**

In this subgroup analysis from ARTESiA, we evaluated the efficacy and safety of apixaban according to baseline CHA<sub>2</sub>DS<sub>2</sub>-VASc score and assessed both the relative and absolute differences in stroke/SE and major bleeding. One in 4 patients in ARTESiA with SCAF had a CHA<sub>2</sub>DS<sub>2</sub>-VASc score >4 and a stroke/SE risk of 2.2% per year. For these patients, the benefits of treatment with apixaban in preventing stroke/SE are greater than the risks. The opposite is true for patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score <4. A substantial intermediate group (CHA<sub>2</sub>DS<sub>2</sub>-VASc=4) exists in which patient preferences will inform treatment decisions.

**Trial registration:** ClinicalTrials.gov (NCT01938248).

**Keywords:** CHA<sub>2</sub>DS<sub>2</sub>-VASc score; apixaban; aspirin; subclinical atrial fibrillation; stroke/systemic embolism; major bleeding

**Abbreviations**

AF=atrial fibrillation

ARR=absolute risk reduction

CI=confidence interval

DOAC=direct oral anticoagulants

HR=hazard ratio

mRS=modified Rankin score

OAC=oral anticoagulant

SCAF=subclinical atrial fibrillation

SE=systemic embolism

## INTRODUCTION

Oral anticoagulation (OAC) to prevent stroke is a pivotal part of treating patients with clinical atrial fibrillation (AF). Vitamin K antagonists, like warfarin, reduce the risk of stroke by 64%.<sup>1</sup> Direct oral anticoagulants (DOACs) are easier to take, safer, further reduce the stroke risk by 20%,<sup>2-4</sup> and are generally preferred for stroke prevention in patients with AF.<sup>5, 6</sup> However, patients with clinical AF who receive OAC have a rate of major bleeding that is 2–3% per year, making it necessary to identify patients in whom the benefits of anticoagulation outweigh the risks.<sup>7, 8</sup> The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was developed to identify a low-risk group of patients with a score of 0 (male) or 1 (female) who have a stroke risk of <1% per year, in whom anticoagulation could be withheld.<sup>9, 10</sup> Current guidelines recommend risk stratification of patients with AF using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and treatment with OAC if stroke risk is >2% per year; with a recommendation to consider OAC if stroke risk is 1–2% per year.<sup>5</sup>

Subclinical AF (SCAF) is defined as short-lasting, asymptomatic AF detected with long-term continuous monitoring with an implantable cardiac device, like a pacemaker or implanted cardioverter defibrillator.<sup>11</sup> While SCAF is associated with an increased risk of stroke, it is associated with lower risk of stroke than clinical AF.<sup>11-13</sup> SCAF is present in over one-third of patients with implanted cardiac pacemakers, defibrillators, or implanted cardiac monitors, making it critical that we understand the risks and benefits of OAC therapy for patients with this condition.<sup>14</sup> The ARTESiA trial demonstrated that oral anticoagulation with apixaban reduced the risk of stroke and systemic embolism (SE) by 37% at a cost of increased bleeding.<sup>15</sup> These results were confirmed by a recent meta-analysis including over 6500 patients with SCAF in which OAC with a DOAC, either apixaban or edoxaban, reduced the risk of stroke/SE by 32%, again with an increase in major bleeding.<sup>16</sup> Thus, while it is clear that OAC reduces stroke due to

SCAF, given the low absolute risk of stroke in this population, risk stratification is needed to understand which patients derive substantial benefit and favorable risk-to-benefit ratio so that practical guidance can be provided for this very common problem.

## **METHODS**

### **ARTESiA Design and Population**

ARTESiA enrolled patients who had SCAF detected by an implanted pacemaker, defibrillator, or cardiac monitor, with at least 1 episode of  $\geq 6$  minutes, but no episodes  $> 24$  hours.<sup>17</sup> Eligible patients had to be at least 55 years of age and have a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 3$ . An early version of the protocol did allow enrollment of a small number of patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2. Patients with prior stroke or age of 75 years or greater could be enrolled, irrespective of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Patients were excluded if they had a history of clinical AF, an ongoing indication for OAC, a history of uncorrected major bleeding in the prior 6 months, or a creatinine clearance  $< 25$  mL/min. The use of open-label dual-antiplatelet therapy was prohibited. The trial protocol was approved by the ethics committee at each site; all the patients provided written informed consent.

Patients were randomized in a double-blind, double-dummy fashion to receive either apixaban 5 mg twice daily (reduced to 2.5 twice daily as indicated by guidelines) or aspirin 81 mg daily. If patients developed clinical AF or SCAF lasting  $> 24$  hours, the protocol recommended that study drug should be stopped and treatment initiated with an open-label anticoagulant.

## Clinical Outcomes

The primary efficacy outcome was a composite of stroke and SE. Randomized groups were compared using the intention-to-treat principle. Patients who developed clinical AF or SCAF lasting >24 hours and permanently discontinued the study drug were censored at the time of clinical AF or SCAF lasting >24 hours. All strokes and transient ischemic attacks (TIAs) were ascertained at the time of each 6 monthly study visits by history, review of relevant medical records, and by administration of the validated stroke questionnaire (QVSFS).<sup>18</sup> Following this process of identifying potential strokes and TIAs, the events were centrally adjudicated by an independent group of neurologists at the Population Health Research Institute. Stroke severity was assessed at the next scheduled study visit using the modified Rankin score (mRS). The primary safety outcome was major bleeding, as defined by the International Society on Thrombosis and Haemostasis.<sup>17</sup>

## Statistical Analysis

In our initial statistical analysis plan we aimed to analyze CHA<sub>2</sub>DS<sub>2</sub>-VASc according to 2 categories ( $\leq 4$  vs.  $>4$ ). However, in order to provide more granular information, more evenly distributed groups, and more transparency of the data, patients were divided into 3 groups based on a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $<4$ , 4, or  $>4$  in the current analysis. Baseline characteristics were summarized as mean $\pm$ standard deviations or median and quartiles for continuous variables and frequencies and percentages for categorical variables. Groups were compared using ANOVA and chi-square tests. Outcomes are presented by treatment and CHA<sub>2</sub>DS<sub>2</sub>-VASc groups as event rates per 100 patient-years of follow-up and number of events. Treatment effects (apixaban vs. aspirin) within each CHA<sub>2</sub>DS<sub>2</sub>-VASc group were estimated using a Cox proportional hazard model with randomized treatment, CHA<sub>2</sub>DS<sub>2</sub>-VASc group, and their interaction. The absolute

risk reduction (ARR) at 3.5 years (the median follow-up for the trial) was estimated as the difference between cumulative incidence at 3.5 years in the apixaban arm minus the cumulative incidence at 3.5 years in the aspirin arm. Confidence intervals for the ARR were derived using the Aalen estimator of the standard error of the cumulative incidence.<sup>19</sup> The heterogeneity in ARR across levels of CHA<sub>2</sub>DS<sub>2</sub>-VASc was tested by a 2-degree of freedom chi square test for pairwise differences in ARR between 3 categories of CHA<sub>2</sub>DS<sub>2</sub>-VASc score. The number needed to treat to benefit or harm were estimated as 1/ARR with confidence intervals obtained by inverting the confidence limits of the ARR. Confidence intervals for the number needed to treat are reported following recommendations.<sup>20</sup> Cumulative incidences were estimated accounting for the competing risk of death using the Gray test.<sup>21</sup> Stroke and major bleeding severity are presented as frequencies and percentages by randomized treatment and CHA<sub>2</sub>DS<sub>2</sub>-VASc group. All analyses were performed with SAS System version 9.4 (TS1M7) (SAS Institute, Inc., Cary, NC).

## RESULTS

### Baseline Characteristics

The CHA<sub>2</sub>DS<sub>2</sub>-VASc distribution is shown in **Figure 1**. CHA<sub>2</sub>DS<sub>2</sub>-VASc score was <4 in 1578 (39.4%), =4 in 1349 (33.6%), and >4 in 1085 (27.0%) patients. Baseline characteristics are presented in **Table 1**; the mean age was 76.8±7.6 years and 36.1% were women. The median duration of the longest SCAF episode in the 6 months prior to study enrollment was 1.47 (0.2, 4.95) hours. Higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score was associated with older age and a greater prevalence of comorbidities (**Table 1**).

### Treatment Effect of Apixaban versus Aspirin According to CHA<sub>2</sub>DS<sub>2</sub>-VASc Categories

In patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score <4, the rate of stroke/SE was 0.85% per year with apixaban and 0.97% per year with aspirin (hazard ratio [HR] 0.87; 95% confidence interval [CI] 0.5–1.52). The rate of major bleeding was 1.4% per year with apixaban and 1.1% per year with aspirin (HR 1.27; 95% CI 0.8–2.1). In this group, over a period of the 3.5 years, apixaban prevented 0.04 (-1.85 to 1.94) strokes/SE per 100 patients compared with aspirin and caused 1.28 (-0.98 to 3.55) major bleeds per 100 patients, but neither was statistically significant (**Figure 2, Table 2**). In patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score =4, the rate of stroke/SE was 0.54% per year with apixaban and 0.86% per year with aspirin (HR 0.63; 95% CI 0.32–1.27). The rate of major bleeding was 1.2% per year with apixaban and 0.9% per year with aspirin (HR 1.31; 95% CI 0.75–2.29). For these patients, over a period of 3.5 years, apixaban prevented approximately 2.25 (0.31 to 4.19) strokes/SE per 100 patients compared with aspirin and caused 0.05 (-2.03 to 2.14) major bleeds (**Figure 2, Table 2**) per 100 patients compared with aspirin, but the increase in bleeding was not statistically significant. In patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score >4, the rate of stroke/SE was 0.98% per year with apixaban and 2.25% per year with aspirin (HR 0.44; 95% CI 0.25–0.77). The rate of major bleeding was 2.13% per year with apixaban and 1.45% per year with aspirin (HR 1.48; 95% CI 0.89–2.45). In this group, over a period of 3.5 years, apixaban prevented 3.95 (1.19 to 6.72) strokes/SE per 100 patients compared with aspirin and caused 1.70 major bleeds (-1.25 to 4.66) but the increase in bleeding was not statistically significant (**Figure 2, Table 2**).

The relative effect of apixaban compared with aspirin on both stroke/SE and major bleeding was consistent across the 3 CHA<sub>2</sub>DS<sub>2</sub>-VASc groups (p-interaction=0.23 and 0.91) (**Figure 2, Table 2**). While the absolute risk increase in major bleeding was consistent across the 3 CHA<sub>2</sub>DS<sub>2</sub>-VASc groups (p-interaction=0.60), the absolute reduction in stroke/SE was

numerically greater among patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score >4 (p-interaction=0.06) (**Figure 3**). For patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score >4, the number needed-to-treat for benefit (NNTB) after 3.5 years (the median duration of ARTESiA trial follow-up) was 25 (95% CI 15 to 84) to prevent 1 stroke/SE and the number needed-to-harm (NNTH) to cause 1 major bleed was 59 (95% CI NNTH 21 to ∞ to NNTB 80) (**Tables 3 & 4**).

### **Stroke and Bleeding Severity**

Stroke severity as assessed using the mRS is presented in **Table 3** by CHA<sub>2</sub>DS<sub>2</sub>-VASC categories at baseline. Among patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score <4, a numerically greater proportion of strokes were mild (mRS 0–2) compared with patients with a higher CHA<sub>2</sub>DS<sub>2</sub>-VASC score (**Table 3**). The number of strokes with moderate/severe disability or death (mRS 3–6) prevented with apixaban were 1 for CHA<sub>2</sub>DS<sub>2</sub>-VASC <4, 6 for CHA<sub>2</sub>DS<sub>2</sub>-VASC =4, and 11 for CHA<sub>2</sub>DS<sub>2</sub>-VASC >4. The subcategories of major bleeding according to study treatment are described in **Table 3**. The number of fatal bleeds, symptomatic intracranial hemorrhage, and bleeding requiring blood transfusion were slightly higher in patients assigned to apixaban than aspirin for CHA<sub>2</sub>DS<sub>2</sub>-VASC <4. For patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC scores =4 or >4, the rates of these severe bleeding events were lower in patients assigned to apixaban compared with aspirin.

### **DISCUSSION**

The ARTESiA trial demonstrated that apixaban significantly reduced the risk of stroke/SE in patients with SCAF. However, since the average absolute risk of stroke in patients with SCAF is only 1.0–1.5% per year,<sup>15,16,22</sup> clinicians are seeking more guidance on how to manage these patients.<sup>23, 24</sup> This analysis from ARTESiA shows that the CHA<sub>2</sub>DS<sub>2</sub>-VASC score, the current standard for guiding the treatment of clinical AF, stratifies risk in a way that may be helpful to guide OAC therapy for patients with SCAF.<sup>5</sup> However, instead of a treatment

threshold for clinical AF of 1 in males and 2 in females, our results suggest a threshold of  $>4$  for both sexes to recommend OAC for patients with SCAF, with OAC being reasonable for patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $=4$  (**Central Illustration**). In addition, another recently presented analysis from ARTESiA shows that the risk of stroke/SE among aspirin-assigned patients with a history of stroke or transient ischemic attack is 3.1% per year; suggesting that OAC should be recommended for these patients even if their CHA<sub>2</sub>DS<sub>2</sub>-VASc score is  $\leq 4$ .<sup>25</sup> This observation is consistent with the established literature for clinical AF, in which having 2 CHA<sub>2</sub>DS<sub>2</sub>-VASc points due to a prior stroke or age  $>75$  years is associated with a higher stroke risk than combinations of another 2 risk factors.<sup>10, 26</sup> In ARTESiA only 9% of patients had prior stroke and this could have contributed, at least in part, to the overall lower than expected event rate in the trial. Nonetheless, our results show that CHA<sub>2</sub>DS<sub>2</sub>-VASc can help with stroke risk stratification for SCAF patients, especially for those without prior stroke. Together with a clear recommendation not to use OAC for primary prevention among patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc  $<4$ , the current analysis gives simple evidence-based guidance for the management of nearly 70% of ARTESiA-eligible patients with SCAF.

Prior to the DOAC era, a 1.7% annual risk of stroke was considered the threshold to initiate oral anticoagulation in patients with AF.<sup>27</sup> In the last decade after the AF studies with DOACs, guidelines have recommended oral anticoagulation for patients with an annual stroke risk of 1.0%.<sup>6</sup> This downward shift is consistent with greater safety of DOACs and patient preference, which favors stroke prevention over limiting bleeding.<sup>4,7</sup> The CHA<sub>2</sub>DS<sub>2</sub>-VASc score replaced the CHADS<sub>2</sub> score, as it defined a group of patients (score  $< 1$  in males,  $< 2$  in females) who had an annual stroke/SE risk of  $< 1\%$ , in whom OAC could be avoided due to the minimal absolute benefit. The current AF guidelines recommend OAC for patients with AF and an



estimated annual thromboembolic risk >2% and suggest that it is reasonable to consider OAC when the risk is between 1% and 2% per year (equivalent to CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 in males and 2 in females), where anticoagulation is reasonable to prevent stroke/SE (class of recommendation 2a, level of evidence A).<sup>5</sup> Thresholds to guide OAC therapy have also considered the severity of strokes and bleeding. Before the DOACs, vitamin K antagonist use was associated with a significant increase in the risk of intracranial and fatal bleeding, which is much lower with the DOACs and was numerically low with apixaban than aspirin in the ARTESiA trial. The higher overall rates of major bleeding in patients treated with apixaban when compared with those receiving aspirin was primarily driven by gastrointestinal bleeding events, which were mostly clinically managed and not as severe of other types of bleeding events (**Table 3**). In contrast, around 45% of the strokes in ARTESiA were moderately or severely disabling (mRS of 3–6), and apixaban reduced this risk by half. In ARTESiA, patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of >4 tended to have more of these disabling strokes, while those with a score of <4 had fewer. Thus, our analysis of the severity of strokes and major bleeds reinforces the conclusions made based on overall stroke rates.

The CHA<sub>2</sub>DS<sub>2</sub>-VASc-specific rates of stroke/SE in ARTESiA are remarkably similar to the rates observed in a large, recent observational study of in patients without OAC who had SCAF lasting between 6 min and 23.5 hours.<sup>28</sup> In this report from Kaplan and colleagues,<sup>20</sup> the rate of stroke/SE was around 1% per year among patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3 and 4, while it increased to between 1.5% per year and 2.6% per year in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc of 5 to 9. Thus, the results of this analysis from a randomized trial may be reasonably generalizable. As another recent observational study of 7651 individuals suggests that SCAF remains common and is often not treated with OAC,<sup>29</sup> there is a great opportunity to prevent

stroke among patients with implanted pacemakers, defibrillators, and cardiac monitors. A recent analysis from the NOAH-AFNET 6 trial showed that CHA<sub>2</sub>DS<sub>2</sub>-VASc score did not seem to help in identifying patients with SCAF who might benefit from OAC, however, the low numbers of strokes/SE do not allow a definitive conclusion.<sup>30</sup> While not directly applicable, the results of this analysis from ARTESiA have implications for AF screening and for the management of patients with SCAF detected through long-term monitoring with wearable devices.<sup>14</sup>

Finally, 1 in 4 patients with device-detected SCAF in ARTESiA went on to develop SCAF lasting >24 hours or electrocardiogram-detected AF, half within the following 18.3 months,<sup>15</sup> and many developed additional CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factors. Thus, it is important that patients with SCAF who are not initially treated with OAC are followed clinically and with pacemaker monitoring for the evolution of their stroke risk factors and SCAF. Ongoing research will help determine if additional clinical, echocardiographic, or laboratory markers can help further refine the estimates of stroke/SE risk and more precisely guide therapy. However, for now, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score provides a reasonable starting point.

### **Limitations**

ARTESiA enrolled fewer patients with a history of stroke compared with earlier observational/registry studies.<sup>11,31</sup> Thus, the lower than expected number of patients with prior stroke would tend to underestimate the overall rate of stroke and embolism, and absolute reduction in stroke/SE with apixaban. However, the magnitude of this effect would be less than 0.1–0.2% per year. Based on the results of the ASSERT trial,<sup>11,32</sup> the use of open-label OAC to treat patients once AF progressed >24 hours would also tend to reduce both the control group rate of stroke/SE and the absolute reduction in this composite with apixaban.<sup>11,12,33</sup> Finally, we recognize that the censoring approach can create informative censoring in patients who

permanently discontinued the study drug; however, a sensitivity analysis adjusting for the factors associated with such censoring produced similar overall results. While all these factors could impact the decision to use OAC for the  $\text{CHA}_2\text{DS}_2\text{-VASc} = 4$  group, they would not affect recommendations for the other two groups ( $\text{CHA}_2\text{DS}_2\text{-VASc} > 4$  and  $< 4$ ). ARTESiA was not powered to detect heterogeneity of effects across subgroups of  $\text{CHA}_2\text{DS}_2\text{VASc}$  and non-significant statistical tests should be interpreted with caution due to the increase probability of false-negative results.

### **Conclusions**

One in 4 patients with SCAF had a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score  $> 4$  and a stroke/SE risk of over 2.2% per year. These patients should generally be treated with OAC, as it appears to prevent nearly twice as many strokes/SE compared with the major bleeds that it causes. Patients with a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score  $< 4$  are unlikely to benefit from OAC as they have a low risk of stroke and this treatment causes more major bleeds than it prevents stroke/SE. A substantial intermediate group ( $\text{CHA}_2\text{DS}_2\text{-VASc} = 4$ ) exists in which patient preferences may help inform treatment decisions.

## **Clinical Perspective**

**Competency in Patient Care:** Subclinical atrial fibrillation (SCAF) is common in patients with implanted devices. Identifying patients who benefit the most from oral anticoagulation is needed in clinical practice.

**Translational Outlook:** CHA<sub>2</sub>DS<sub>2</sub>-VASc score, the current standard for guiding the treatment of clinical AF, helps in guiding oral anticoagulation for patients with SCAF.

Journal Pre-proof

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**Figure Legends****Figure 1. CHA<sub>2</sub>DS<sub>2</sub>-VASc distribution.**

Distribution of patients according to CHA<sub>2</sub>DS<sub>2</sub>-VASc categories.

**Figure 2. Treatment effect on stroke/SE and major bleeding according to CHA<sub>2</sub>DS<sub>2</sub>-VASc categories.**

Treatment effect of apixaban versus aspirin for stroke/SE and major bleeding according to CHA<sub>2</sub>DS<sub>2</sub>-VASc categories. Rates per 100 patient-years of follow-up, absolute risk reduction based on difference in cumulative incidence (%) at 3.5 years.

**Figure 3. Stroke/SE and major bleeding according to CHA<sub>2</sub>DS<sub>2</sub>-VASc categories and treatment.**

Kaplan-Meier curves of stroke/SE and major bleeding according to CHA<sub>2</sub>DS<sub>2</sub>-VASc categories in patients assigned to apixaban or aspirin.

**Central Illustration. ARTESiA: apixaban versus aspirin in patients with subclinical AF.**

Treatment benefit according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

**Table 1. Patient characteristics by CHA<sub>2</sub>DS<sub>2</sub>-VASc level**

Characteristic	CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	CHA <sub>2</sub> DS <sub>2</sub> -VASc=4	CHA <sub>2</sub> DS <sub>2</sub> -VASc >4
	(N=1578)	(N=1349)	(N=1085)
Age, mean (SD), yrs	74.9 (8.1)	77.4 (7.4)	78.8 (6.4)
CHA <sub>2</sub> DS <sub>2</sub> -VASc components, no. (%)			
Congestive heart failure	260 (16.5)	336 (24.9)	541 (49.9)
Hypertension	1026 (65.0)	1216 (90.1)	1027 (94.7)
Age ≥75 years	841 (53.3)	948 (70.3)	877 (80.8)
Diabetes mellitus	243 (15.4)	366 (27.1)	558 (51.4)
Stroke, systemic embolism, or TIA	20 (1.3)	48 (3.6)	293 (27.0)
Vascular disease	346 (21.9)	560 (41.5)	762 (70.2)
Coronary artery disease	293 (18.6)	508 (37.7)	684 (63.0)
Peripheral artery disease	72 (4.6)	101 (7.5)	161 (14.8)
Aortic plaque	31 (2.0)	34 (2.5)	41 (3.8)
Age 65–74 years	567 (35.9)	330 (24.5)	189 (17.4)
Sex category (Female)	344 (21.8)	595 (44.1)	508 (46.8)
Baseline antiplatelet use, no. (%)			
Aspirin	776 (49.2)	802 (59.5)	724 (66.7)
Other single antiplatelet agent	23 (1.5)	44 (3.3)	91 (8.4)
Dual antiplatelet therapy	30 (1.9)	37 (2.7)	70 (6.5)
History of major bleeding >6 months before enrollment, no. (%)	27 (1.7)	31 (2.3)	39 (3.6)
Device type, no. (%)			
Pacemaker	1185 (75.1)	958 (71.0)	641 (59.1)
ICD	191 (12.1)	177 (13.1)	186 (17.1)
CRT-ICD or CRT pacemaker	115 (7.3)	145 (10.7)	205 (18.9)
ICM	87 (5.5)	69 (5.1)	53 (4.9)
Longest episode of SCAF in past 6 months, no./No. (%)			
No episodes	253/1577 (16.0)	219/1347 (16.3)	160/1083 (14.8)
<6 min	35/1577 (2.2)	27/1347 (2.0)	23/1083 (2.1)
6 min to <1 hour	398/1577 (25.2)	338/1347 (25.1)	296/1083 (27.3)
1 to <6 hours	553/1577 (35.1)	481/1347 (35.7)	390/1083 (36.0)

Characteristic	CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	CHA <sub>2</sub> DS <sub>2</sub> -VASc=4	CHA <sub>2</sub> DS <sub>2</sub> -VASc >4
	(N=1578)	(N=1349)	(N=1085)
6 to <12 hours	215/1577 (13.6)	194/1347 (14.4)	142/1083 (13.1)
12 to 24 hours	123/1577 (7.8)	88/1347 (6.5)	72/1083 (6.6)
Weight, mean (SD), kg	84.4 (17.8)	81.6 (18.9)	81.6 (17.9)
Blood pressure, mean (SD), mm Hg			
Systolic	134.8 (18.1)	135.5 (19.3)	134.7 (19.0)
Diastolic	76.6 (10.2)	75.7 (10.5)	73.5 (10.3)
Creatinine clearance, mean (SD), mL/min	78.9 (31.1)	69.2 (27.5)	63.3 (23.3)
Met criteria for reduced-dose dose apixaban	77 (4.9)	160 (11.9)	137 (12.6)
Developed clinical AF or SCAF >24 hours during follow-up	457 (29.0)	425 (31.5)	355 (32.7)
Censored at time of clinical AF or SCAF >24 hours*	121 (7.7)	132 (9.8)	87 (8.0)

\*In patients who permanently discontinued the study drug.

CRT=cardiac resynchronization therapy; ICD=implantable cardioverter defibrillator; ICM=implantable cardiac monitor; SCAF=subclinical atrial fibrillation; SD=standard deviation; TIA=transient ischemic attack.

**Table 2. Randomized treatment effect by CHA<sub>2</sub>DS<sub>2</sub>-VASc group at randomization**

Endpoint	Apixaban Events (Rate*)	Aspirin Events (Rate*)	HR (95% CI) (Apixaban vs. Aspirin)	Interaction p-value	Absolute Risk Reduction <sup>†</sup> (Apixaban - Aspirin)	Interaction p-value
Stroke or SE				0.23		0.06
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	24 (0.85)	27 (0.97)	0.87 (0.50, 1.52)		-0.04 (-1.94, 1.85)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc =4	13 (0.54)	21 (0.86)	0.63 (0.32, 1.27)		-2.25 (-4.19, -0.31)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	18 (0.98)	38 (2.25)	0.44 (0.25, 0.77)		-3.95 (-6.72, -1.19)	
ISTH major bleeding				0.91		0.60
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	40 (1.44)	31 (1.11)	1.27 (0.80, 2.03)		1.28 (-0.98, 3.55)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc =4	28 (1.18)	22 (0.90)	1.31 (0.75, 2.29)		0.05 (-2.03, 2.14)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	38 (2.13)	25 (1.45)	1.48 (0.89, 2.45)		1.70 (-1.25, 4.66)	
Stroke, SE, or ISTH major bleeding				0.80		0.24
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	56 (2.04)	51 (1.86)	1.09 (0.74, 1.59)		1.30 (-1.46, 4.07)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc =4	38 (1.62)	39 (1.62)	1.00 (0.64, 1.56)		-1.96 (-4.69, 0.76)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	54 (3.08)	57 (3.43)	0.90 (0.62, 1.31)		-1.20 (-5.06, 2.67)	
Stroke, SE, or death from cardiovascular causes				0.79		0.43
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	46 (1.63)	51 (1.83)	0.89 (0.60, 1.32)		-0.64 (-3.30, 2.03)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc =4	42 (1.75)	48 (1.96)	0.90 (0.59, 1.36)		-2.60 (-5.41, 0.21)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	60 (3.26)	72 (4.27)	0.76 (0.54, 1.07)		-3.52 (-7.68, 0.64)	
Stroke, MI, SE, or all-cause death				0.88		0.93
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	135 (4.83)	134 (4.85)	0.99 (0.78, 1.25)		-1.34 (-5.49, 2.81)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc =4	122 (5.17)	125 (5.15)	1.01 (0.78, 1.29)		-1.89 (-6.23, 2.45)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	162 (8.92)	159 (9.55)	0.93 (0.75, 1.16)		-2.77 (-8.61, 3.07)	

\*Rate per 100 patient-years of follow-up.

<sup>†</sup>Difference in cumulative incidence (%) at 3.5 years.

CI=confidence interval; HR=hazard ratio; ISTH=International Society on Thrombosis and Haemostasis; MI=myocardial infarction; SE=systemic embolism.

**Table 3. Severity of stroke and characteristics of major bleeding by treatment and CHA<sub>2</sub>DS<sub>2</sub>-VASc group at randomization**

<b>Endpoint</b>	<b>Apixaban No. (%)</b>	<b>Aspirin No. (%)</b>	<b>p-value</b>
<b>Stroke Severity (modified Rankin Scale)<sup>1</sup></b>			
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4			0.34
0–2	13 (54.2)	18 (66.7)	
3–6	7 (29.2)	8 (29.6)	
Missing data	4 (16.7)	1 (3.7)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc = 4			0.38
0–2	9 (69.2)	10 (50.0)	
3–6	3 (23.1)	9 (45.0)	
Missing data	1 (7.7)	1 (5.0)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4			0.78
0–2	9 (50.0)	17 (45.9)	
3–6	9 (50.0)	20 (54.1)	
Missing data	0 (0.0)	0 (0.0)	
<b>ISTH Major Bleeding Criteria<sup>2</sup></b>			
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4			
Fatal bleeding	5 (0.63)	5 (0.64)	1.00
Symptomatic intracranial hemorrhage	12 (1.51)	10 (1.28)	0.69
Gastrointestinal bleeding	15 (1.89)	13 (1.66)	0.73
Transfusion	15 (1.89)	13 (1.66)	0.73
CHA <sub>2</sub> DS <sub>2</sub> -VASc = 4			
Fatal bleeding	3 (0.45)	3 (0.44)	1.00
Symptomatic intracranial hemorrhage	2 (0.30)	7 (1.03)	0.18
Gastrointestinal bleeding	15 (2.24)	8 (1.18)	0.13
Transfusion	11 (1.64)	11 (1.62)	0.97
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4			
Fatal bleeding	2 (0.36)	6 (1.12)	0.17
Symptomatic intracranial hemorrhage	3 (0.55)	6 (1.12)	0.34
Gastrointestinal bleeding	25 (4.55)	10 (1.87)	0.01

<b>Endpoint</b>	<b>Apixaban No. (%)</b>	<b>Aspirin No. (%)</b>	<b>p-value</b>
Transfusion	9 (1.64)	7 (1.31)	0.65

\*Percentages computed over the total number of events in each CHA<sub>2</sub>DS<sub>2</sub>-VASc group.

†Percentages computed over the total number of patients in each CHA<sub>2</sub>DS<sub>2</sub>-VASc group.

ISTH=International Society on Thrombosis and Haemostasis.

Journal Pre-proof

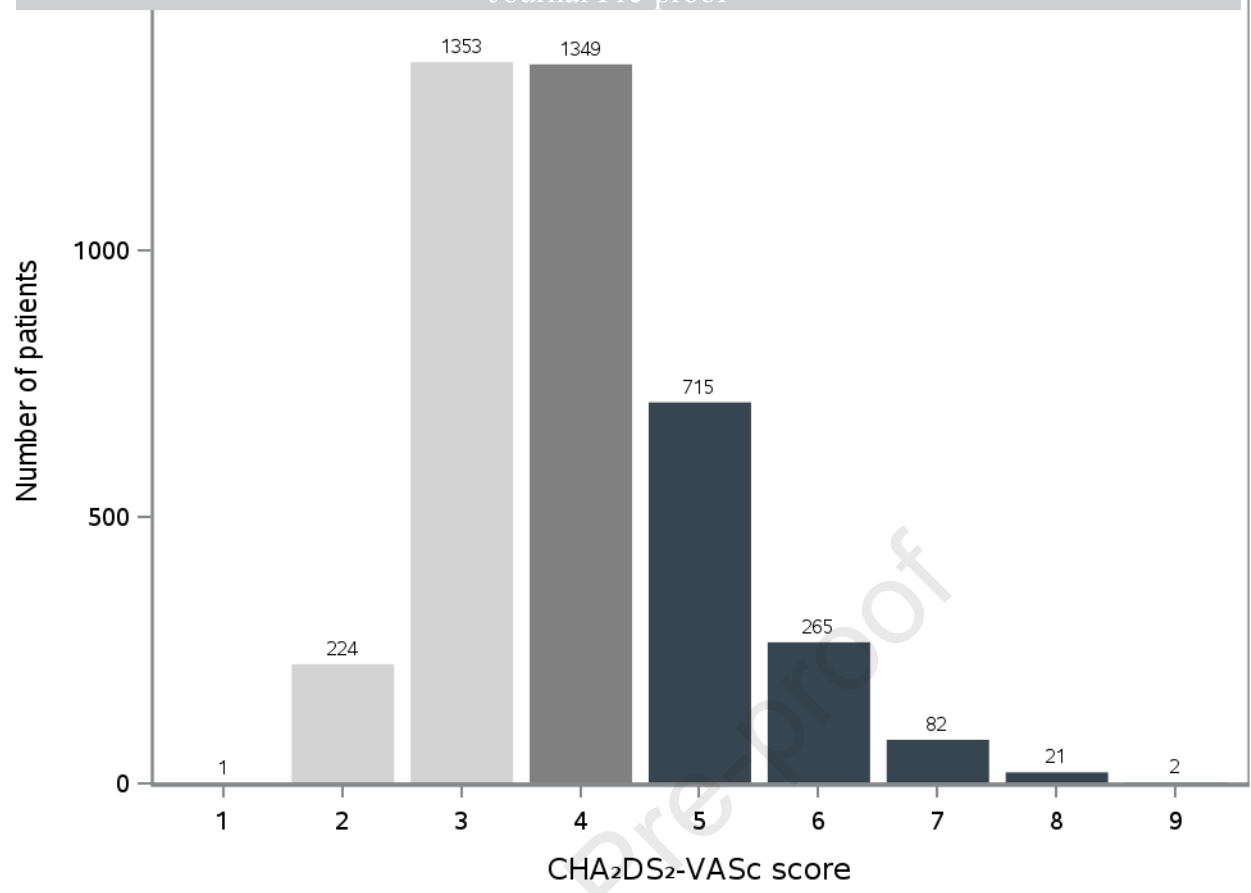
**Table 4. Number needed to treat to benefit/harm after 3.5-years of follow-up by CHA<sub>2</sub>DS<sub>2</sub>-VASc group at randomization**

<b>Endpoint</b>	<b>Number Needed to Treat to Benefit/Harm after 3.5 Years of Follow-up* (95% CI)</b>
Stroke or SE	
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	NNTB 2314 (NNTB 52 to ∞ to NNTH 54)
CHA <sub>2</sub> DS <sub>2</sub> -VASc =4	NNTB 44 (24 to 324)
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	NNTB 25 (15 to 84)
ISTH major bleeding	
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	NNTH 78 (NNTH 28 to ∞ to NNTB 102)
CHA <sub>2</sub> DS <sub>2</sub> -VASc =4	NNTH 1852 (NNTH 47 to ∞ to NNTB 49)
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	NNTH 59 (NNTH 21 to ∞ to NNTB 80)
Stroke, SE, or ISTH major bleeding	
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	NNTH 77 (NNTH 25 to ∞ to NNTB 68)
CHA <sub>2</sub> DS <sub>2</sub> -VASc =4	NNTB 51 (NNTB 21 to ∞ to NNTH 132)
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	NNTB 84 (NNTB 20 to ∞ to NNTH 37)
Stroke, SE, or death from cardiovascular causes	
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	NNTB 157 (NNTB 30 to ∞ to NNTH 49)
CHA <sub>2</sub> DS <sub>2</sub> -VASc =4	NNTB 38 (NNTB 18 to ∞ to NNTH 472)
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	NNTB 28 (NNTB 13 to ∞ to NNTH 155)
Stroke, MI, SE, or all-cause death	
CHA <sub>2</sub> DS <sub>2</sub> -VASc <4	NNTB 75 (NNTB 18 to ∞ to NNTH 36)
CHA <sub>2</sub> DS <sub>2</sub> -VASc =4	NNTB 53 (NNTB 16 to ∞ to NNTH 41)
CHA <sub>2</sub> DS <sub>2</sub> -VASc >4	NNTB 36 (NNTB 12 to ∞ to NNTH 33)

\*Number needed to treat to benefit: Number of patients needed to be treated for 1 additional patient to benefit. Number needed to treat to harm: Number of patients needed to be treated for 1 additional patient to be harmed. Confidence intervals for non-significant absolute risk reductions include scenarios of both benefit and harm and should be interpreted with caution.

CI=confidence interval; ISTH=International Society on Thrombosis and Haemostasis; MI=myocardial infarction; NNTB=number needed to treat to benefit; NNTH=number needed to treat to harm; SE=systemic embolism.





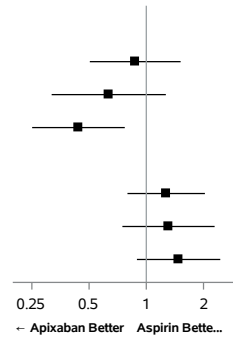
Outcome

Stroke or systemic embolism

CHA2DS2-VASc	Apixaban	Aspirin	Relative Risk (95% CI)
< 4	24 (0.85)	27 (0.97)	0.87 (0.50, 1.52)
= 4	13 (0.54)	21 (0.86)	0.63 (0.32, 1.27)
> 4	18 (0.98)	38 (2.25)	0.44 (0.25, 0.77)

ISTH Major Bleeding

CHA2DS2-VASc	Apixaban	Aspirin	Relative Risk (95% CI)
< 4	40 (1.44)	31 (1.11)	1.27 (0.80, 2.03)
= 4	28 (1.18)	22 (0.90)	1.31 (0.75, 2.29)
> 4	38 (2.13)	25 (1.45)	1.48 (0.89, 2.45)



p-value

0.23
-0.04 (-1.94, 1.85)
-2.25 (-4.19, -0.31)
-3.95 (-6.72, -1.19)

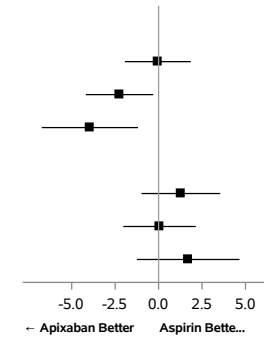
0.91

1.28 (-0.98, 3.55)
0.05 (-2.03, 2.14)
1.70 (-1.25, 4.66)

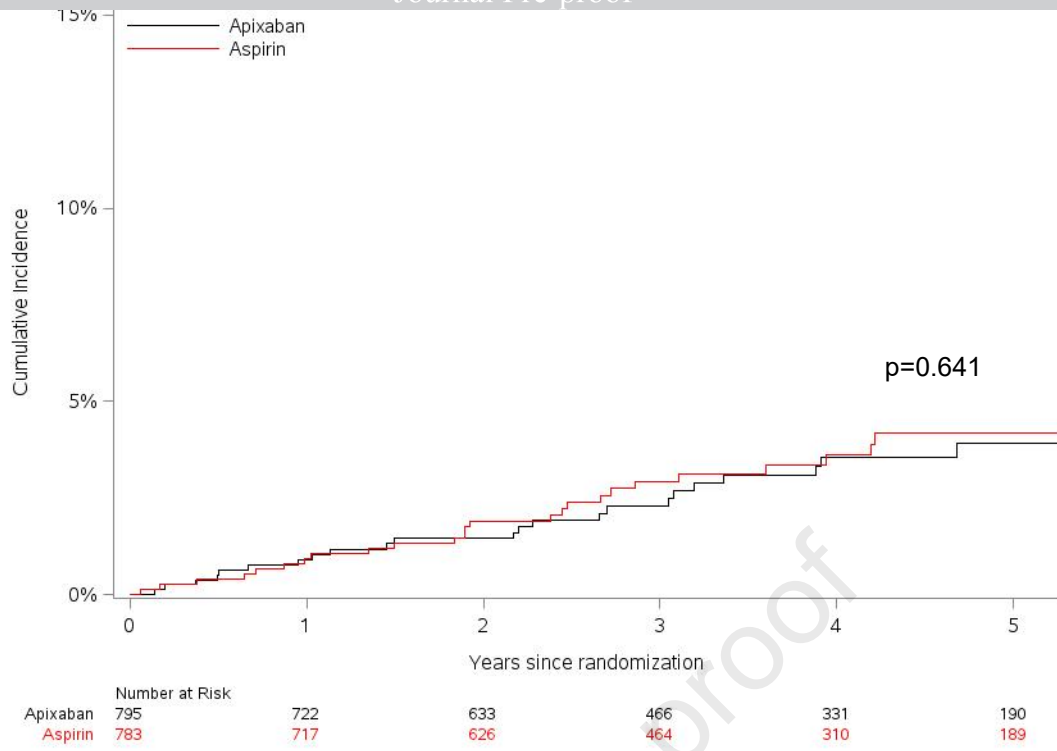
Interaction p-value

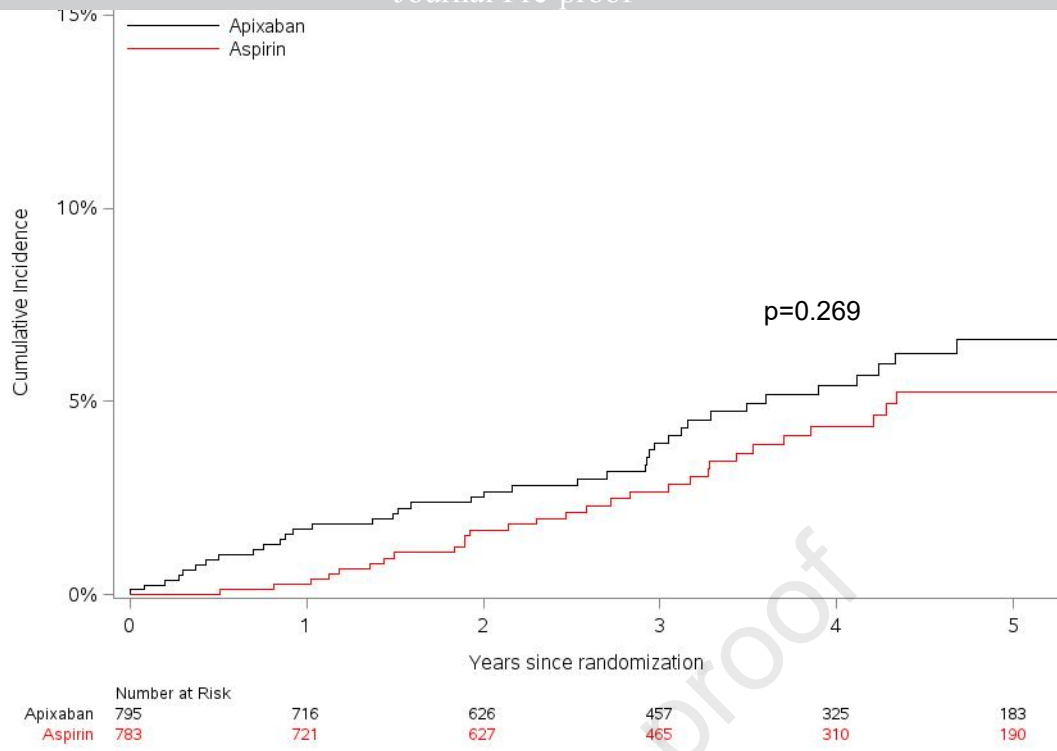
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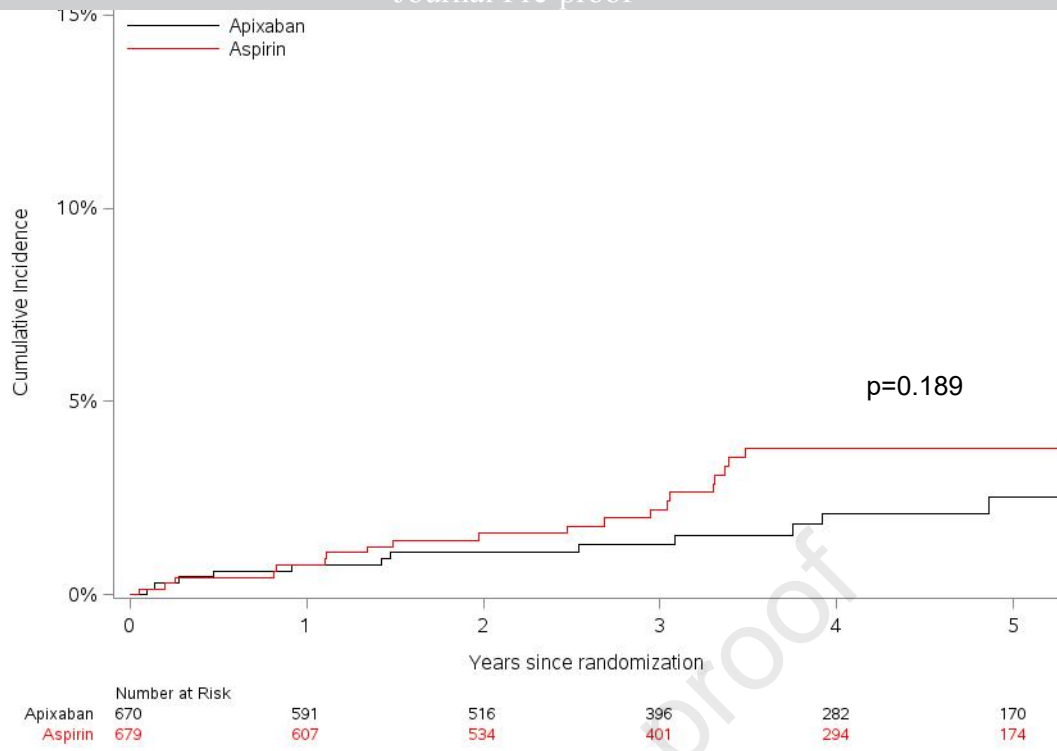
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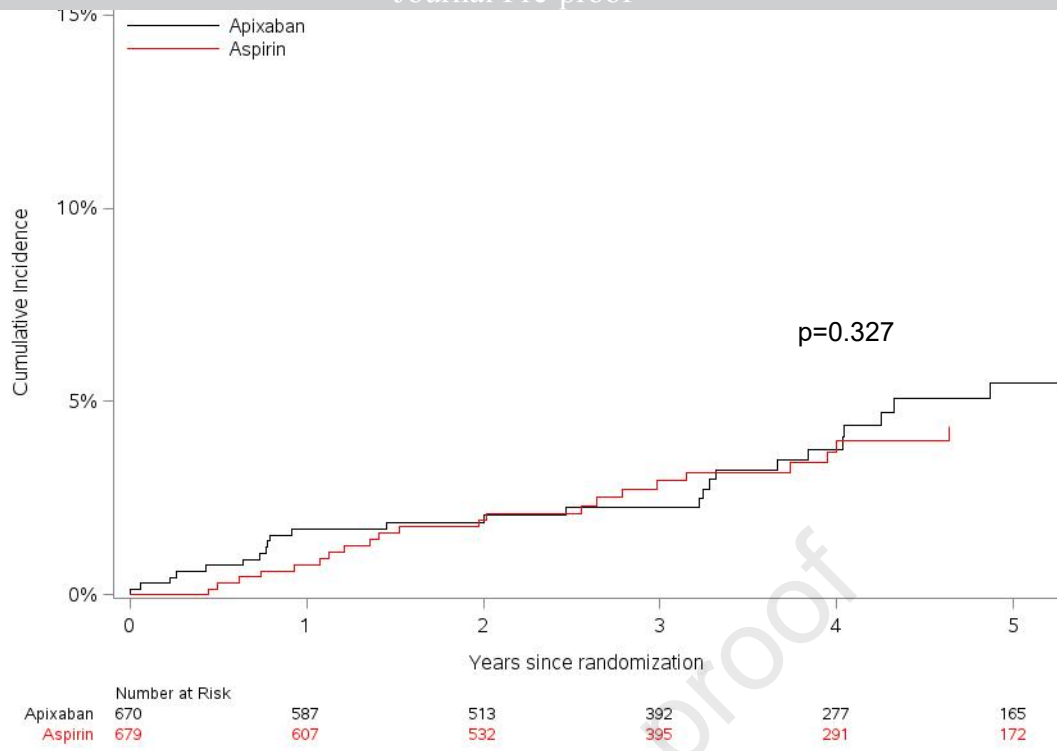


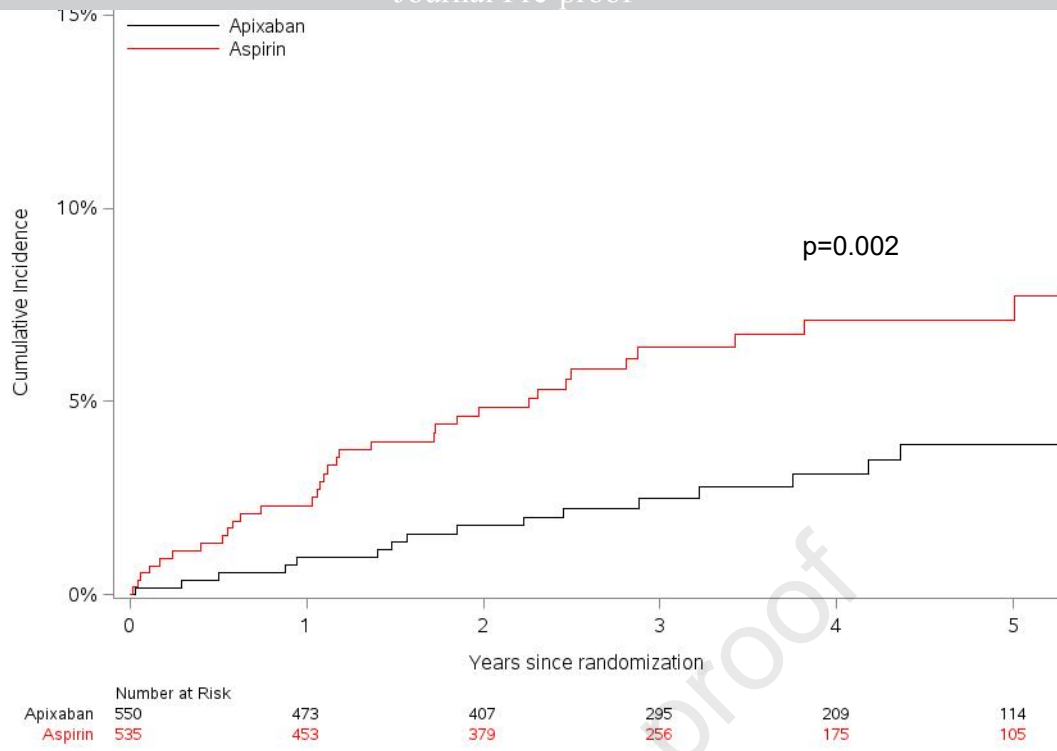
Journal Pre-proof

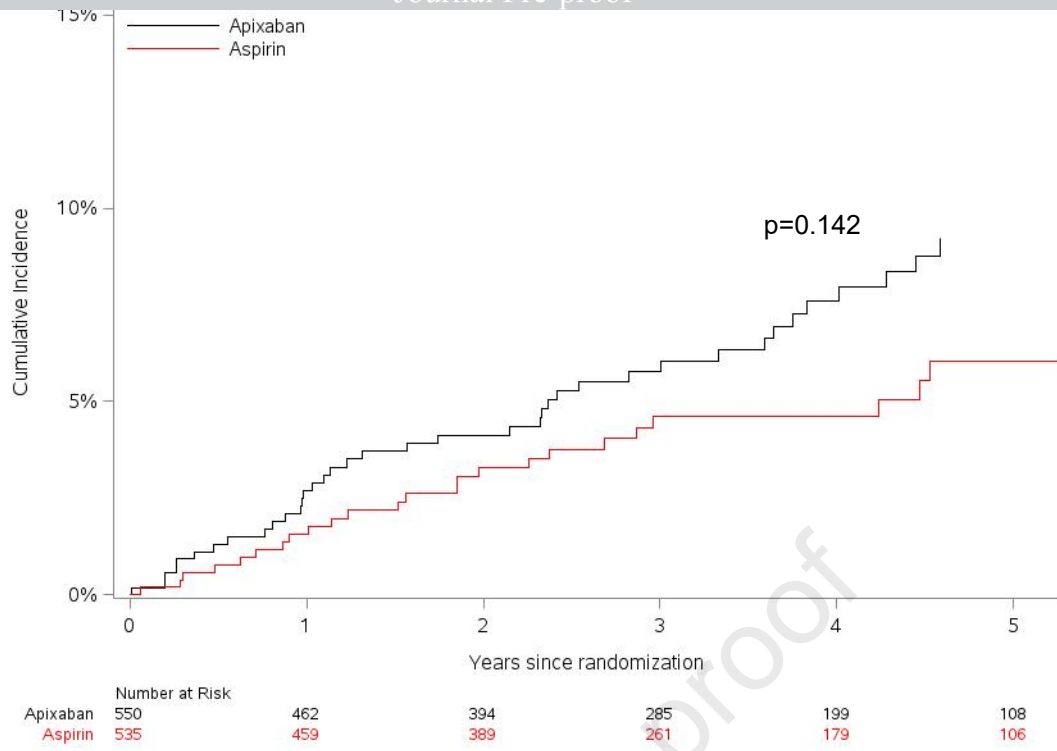




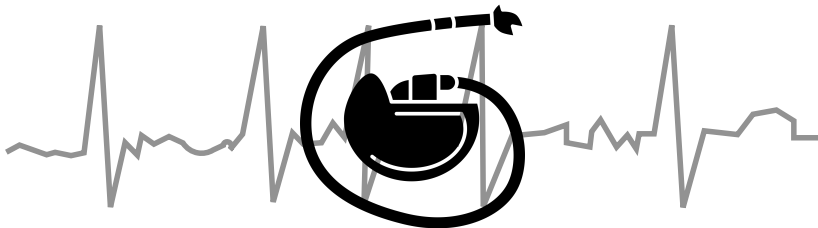




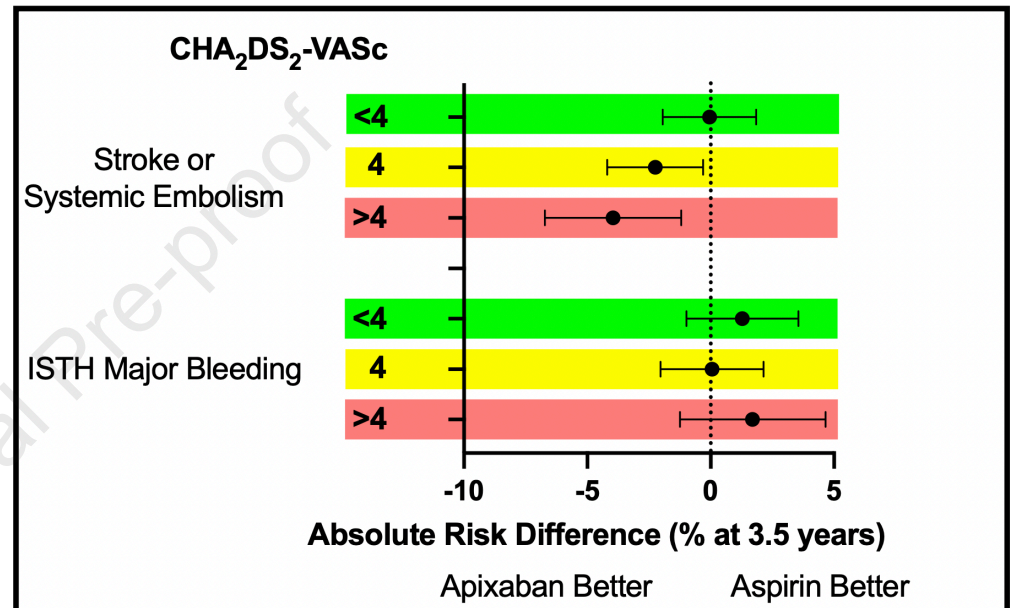








Patients with Device-Detected  
Subclinical Atrial Fibrillation  
In the ARTESiA Trial



CHA<sub>2</sub>DS<sub>2</sub>-VASc < 4

Low risk of stroke

Bleeding risk outweighs benefit

CHA<sub>2</sub>DS<sub>2</sub>-VASc = 4

Intermediate risk of stroke

Similar risk and benefit

CHA<sub>2</sub>DS<sub>2</sub>-VASc > 4

High risk of stroke

Stroke benefit outweighs risk