Gender difference in left atrial appendage occlusion outcomes: Results from the Amplatzer™ Amulet™ Observational Study

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Abstract
Background: Percutaneous LAAO represents an alternative for stroke prevention in patients not tolerating anticoagulation. While women are at higher risk of complications during percutaneous coronary or valvular interventions, the impact of gender on LAAO outcomes is not well characterized. The current study assessed potential gender-related differences in procedural and long-term outcomes following left atrial appendage occlusion (LAAO).

Methods: 1088 AF patients were enrolled in the prospective, multicenter, Amplatzer™ Amulet™ Observational Study and followed for 2 years with scheduled adverse event assessments. The prespecified primary outcome was ischemic stroke, systemic embolism or cardiovascular (CV) death at 2 years. We also compared the rate of procedural success, device-related thrombus (DRT) and major bleeding between genders.

Results: 702 men and 386 women underwent LAAO. Implant success was high, and similar between men and women (98.9 vs 99.5%, p = 0.58). Similarly, no difference was observed in the primary outcome (12.0 vs 12.5%, p = 0.82). Compared to the CHA2DS2-VASc predicted rate, we observed a numerically greater absolute risk reduction of ischemic stroke in women (from 7.6 to 2.1%/year) than men (from 6.2 to 2.2%/year). DRT through 2 years was similar between groups (1.6%, p = 0.96). We found no significant gender difference in terms of periprocedural or long-term (7.1 vs 7.6%/year) major bleeding.

Conclusions: In this large group of patients undergoing LAAO using the Amplatzer™ Amulet™ device we found no significant gender difference in terms of procedural or long-term clinical outcomes. Similarly to oral anticoagulation, device-based LAA occlusion renders AF-related stroke risk similar in women and men.

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1. Introduction

Oral anticoagulation represents the first choice of stroke prevention in the setting of atrial fibrillation (AF) [1]. However, despite the increasing use of direct oral anticoagulants, still a substantial proportion of AF patients are not good candidates for long-term anticoagulant therapy, either for excessive bleeding risk, intolerance or the patient’s refusal. For this reason, over the past...
decade percutaneous left atrial appendage occlusion (LAAO) has progressively expanded in the setting of AF-related stroke prevention.

Stroke risk in AF is commonly assessed by using the CHA2DS2-VASc score, which includes female gender as a risk factor conferring 1 point, especially in the presence of ≥2 additional stroke risk factors [2]. More importantly, women are more likely to suffer a thromboembolic event or ischemic stroke when anticoagulation is not adequate, but have a similar thromboembolic risk profile when adequately anticoagulated, highlighting the importance of adherence to an anticoagulation regimen [3]. On the other hand, women have a higher risk of periprocedural adverse events and bleeding complications during and after percutaneous coronary intervention (PCI) than men [4–7]. Similarly, previous studies have clearly shown that women have a higher risk of periprocedural complication in the setting of transcatheter aortic valve intervention despite similar long-term outcomes [8,9].

The objective of the present analysis is to investigate potential gender-related differences in procedural and long-term clinical outcomes following LAAO from the large prospective, multicenter, global Amplatz® Amulet® Observational Study [10].

2. Methods

Briefly, the prospective observational study enrolled 1,088 patients undergoing LAAO using Amplatz® Amulet® device at 61 clinical centers worldwide. The study is registered on ClinicalTrials.gov (NCT02447081). The authors were able to query all data and had final authority over the publication. Written informed consent was obtained following local ethics board approval. The study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

2.1. Study population

Patients had a history of non-valvular AF, either paroxysmal or persistent, and were eligible for catheter-based LAAO according to standard indications [11]. Exclusion criteria included evidence of an intracardiac thrombus, active infection of LAA anatomy, or the inability to deliver the device according to the sizing chart. For the purpose of this sub-analysis, patients were divided into two groups according to gender. Baseline clinical characteristics, peri-procedural outcomes, and clinical follow-up through 2 years post-LAAO were compared between groups.

2.2. Left atrial appendage closure procedure

Echocardiography ruled out LAA thrombosis and assessed LAA size and shape. The procedure was guided with transesophageal (TEE) or intracardiac echocardiography at the operator’s discretion. The procedure was performed as previously described [12]. Color flow Doppler assessed peri-device flow at the conclusion of the procedure. The post-procedural antithrombotic consisted of protocol recommended aspirin (or an alternative antiplatelet) for 6 months post-implant and clopidogrel per standard of care, but was ultimately at the physician’s discretion.

2.3. Echocardiographic and clinical follow up

Medication and adverse event assessments were performed prior to discharge, at 1–3 months, 6 months, 12 months, and 2 years follow-up. Adverse events were reviewed and adjudicated by an independent clinical events committee (physicians with relevant expertise not participating in the study). The committee attributed deaths as due to cardiovascular (CV), non-CV, or unknown causes. In alignment with the Munich consensus document for percutaneous LAAO reporting, deaths of unknown causes are conservatively reported as CV deaths in this analysis [13]. Transthoracic echocardiogram was acquired pre-discharge to evaluate for device embolization or pericardial effusion. A TEE was performed 1–3 months post-LAAO to assess the presence of device-related thrombosis (DRT) and peri-device leak. DRT was defined as diffuse (>50% of the disc surface covered by thrombus), mobile (thrombus motion in at least 3 sequential frames [11], laminar (basal length > height) or pedunculated (height > basal length). Peri-device leak was categorized as none, small (<3 mm), medium (3–5 mm), or large (>5 mm). The threshold for clinically adequate sealing in the current study was residual flow < 3 mm. Procedural and follow-up echocardiograms were assessed by an independent centralized core laboratory.

2.4. Procedural and long-term outcome

Technical success was defined as the successful deployment and implantation of the device within the LAA. Procedural success was defined as technical success without major adverse event during hospitalization. Major adverse events include death, stroke, embolism, pericardial or other major bleeding requiring intervention, device embolization, and major vascular complications.

The prespecified primary outcome of the study was a composite of ischemic stroke, systemic embolism, or CV death at 2 year follow up. In addition, all-cause mortality, cerebrovascular events, DRT and major bleeding are reported. Cerebrovascular events were classified as ischemic or hemorrhagic stroke and transient ischemic attack (TIA). In case of stroke or TIA, the protocol required that sites obtain a TEE to evaluate for DRT. Major bleeding was defined as 3 or greater according to BARC definition [14]. All adverse events, regardless of temporal relationship, were adjudicated for relationship to the procedure and device.

2.5. Statistical analysis

Baseline clinical characteristics and medication regimen were summarised using descriptive statistics. Percentages were used to summarise categorical variables and mean and standard deviation (SD) were used to summarize continuous variables. Baseline and procedural characteristics were compared using the Wilcoxon Rank Sum or Fischer’s Exact Test. Kaplan-Meier estimates were utilised to calculate the clinical event rates of the composite primary outcome, death, and DRT at 2 years and compared between groups with the Log-Rank Test. The incidence rates for all other clinical events were calculated as annualized rates (events/patient-years) and compared between groups with a Poisson regression model. The annualized rates of ischemic stroke across a range of CHA2DS2-VASc scores in AF patients not treated with OAC were utilized to predict the rate of stroke in the current study using baseline CHA2DS2-VASc scores [15]. Similarly, the annualized rates of major bleeding across a range of HAS-BLED scores in AF patients treated with warfarin were utilized to predict the rate of major bleeding in the current study using baseline HAS-BLED scores [16]. SAS version 9.4 (SAS Institute, Cary, North Carolina) was used for analysis and STATA/SE version 15.1 (StataCorp, College Station, Texas) for graphing.

3. Results

3.1. Patient characteristics

A total of 1114 patients were consented and screened while 1088 proceeded to enrollment and underwent an implant attempt.
with the Amulet device. Three patients with intracardiac thrombus identified on baseline imaging proceeded with device implantation at the physician’s discretion despite being exclusionary. Baseline clinical characteristics and demographics are reported in Table 1. The proportion of enrolled patients in terms of gender was nearly 2:1 (702 men and 386 women). Men were younger and more likely to have history of congestive heart failure or previous coronary revascularization. The CHA2DS2-VASc score was greater in women, whereas the HAS-BLED score was lower in women. The indication for the LAAO procedure was most often a contraindication to oral anticoagulation, with a similar proportion (83%) of both genders contraindicated to anticoagulation.

3.2. Peri-procedural characteristics and outcomes

Procedural characteristics and acute outcomes (≤7 days) are presented in Table 2. Technical and procedural success were very high and did not differ by gender. Heparin use was higher in men than women, but with similar intraprocedural ACT value. While total procedural time was similar, contrast use was higher in men than women. No difference in terms of post-procedural antithrombotic therapy between men and women were observed (Fig. 1), with 57.1 vs 58.9% of patients discharged on dual antiplatelet therapy and 23.4 vs 20.7% on single antiplatelet therapy, with similar rates of transitioning to mostly single antiplatelet therapy at 1–3 months, and eventual antithrombotic therapy desescalation through the 2 years of follow-up after LAAO. Details of patients discharged on anticoagulation regimens are presented in Table 3. Non-vitamin K antagonist oral anticoagulants were prescribed more often than vitamin K antagonist oral anticoagulants in both genders.

Peri-procedural mortality was similar between groups (1 men and 2 women, p = 0.26), all due to CV causes but only one clearly related to LAAO (cardiac tamponade). Four patients reported a peri-procedural ischemic stroke (1 men and 3 women, 0.1 vs 0.8%, p = 0.09), with only one stroke considered disabling. No hemorrhagic stroke, TIA or systemic embolism were observed. Major vascular complications were similar between the two groups (1.3 vs 1.3%). Overall, the rate of peri-procedural adverse events did not differ between the two groups (3.9 vs 4.4%, p = 0.49). Peri-procedural or device-related bleeding were lower in men than women (2.6% vs 3.6%) but this difference did not reach a statistical significance (p = 0.32). No peri-procedural thromboembolic events were reported in the 3 subjects with baseline LAAO thrombus.

3.3. Long-term clinical outcomes

The final 2 year follow-up visit was completed in 864 subjects. Reasons for not completing a 2 year visit include death (n = 161), withdrawal from the study (n = 40), or lost-to-follow-up (n = 15). Table 4 presents long-term clinical outcomes through the 2 year follow-up visit. The rate of primary outcome did not differ between men and women (12.0 vs 12.5%, p = 0.82 respectively) (Fig. 2A). Similarly, no difference in terms of CV mortality (9.0 vs 9.0%, p = 0.91, respectively) or all-cause mortality (15.6 vs 14.5, p = 0.53, respectively) were observed between genders at 2 year follow-up (Fig. 2B & 2C). The observed annualized rate (events/patient-years) of ischemic stroke did not differ between men and women (2.2 vs 2.1%/year, respectively) with a consistent reduction with respect of the CHA2DS2-VASc predicted rate (6.2 vs 7.6%/year, respectively) (Fig. 3). The 95% confidence intervals of ischemic stroke reduction compared to the predicted rate were (48%, 77%) for males and (54%, 84%) for females. The rate of DRT were identical between men and women (1.6%, p = 0.96). The annualized rates of major bleeding events were similar between genders (7.1 vs 7.6%/year, p = 0.69), which was comparable to the HAS-BLED predicted rates (6.8%/year for men and 6.6%/year for women).

4. Discussion

Gender differences play a role in the incidence and clinical presentation of cardiovascular diseases as well as in the efficacy and safety of antithrombotic treatment. The pathophysiological mechanisms underlying these gender-related effects are not fully understood, and are likely to be multifactorial. Women are at higher risk of stroke than men in the setting of atrial fibrillation, possibly due to older age, under-treatment with anticoagulant therapy and poor anticoagulation control [2]. Conversely, in the setting of percutaneous intervention, either coronary or structural, female gender is associated with a higher bleeding risk than men [4–9]. In the present paper, among 1,088 patients referred to LAAO and prospectively enrolled in the Amplatzer™ Amulet™ Observational Study, we found no significant gender difference in terms of clinical indication, procedural outcome (both efficacy and safety), post-procedural antithrombotic therapy and long-term clinical outcomes.

4.1. LAAO compared to other interventions

Several multicentre registries of PCI have consistently shown that women show an augmented bleeding hazard [4–7,17–21].

Table 1

| Age (years) | All Enrolled (n = 1088) | Male (n = 702) | Female (n = 386) | p-value |
|------------|-----------------------|---------------|-----------------|--------|
| Atrial fibrillation at time of implant | 75.2 ± 8.5 | 74.6 ± 8.7 | 76.2 ± 7.9 | 0.01 |
| Hypertension | 59.5% (647) | 61.5% (702) | 57.7% (215) | 0.06 |
| Congestive heart failure | 82.3% (913) | 84.5% (953) | 82.9% (320) | 0.55 |
| Previous stroke | 17.2% (187) | 19.8% (139) | 14.7% (215) | <0.01 |
| Previous transient ischemic attack | 27.5% (299) | 28.8% (202) | 25.1% (97) | 0.20 |
| Previous major bleed | 10.6% (115) | 73.6% (517) | 68.1% (263) | 0.06 |
| Previous percutaneous coronary intervention or coronary artery bypass grafting | 25.5% (277) | 30.1% (211) | 17.1% (66) | <0.0001 |
| Peripheral vascular disease (peripheral artery or venous disease) | 15.3% (167) | 15.7% (110) | 14.8% (57) | 0.73 |
| CHA2DS2-VASc Score | 4.2 ± 1.6 | 3.9 ± 1.6 | 4.7 ± 1.5 | <0.0001 |
| HAS-BLED Score | 3.3 ± 1.1 | 3.4 ± 1.1 | 3.2 ± 1.0 | 0.01 |
| Contraindication to oral anticoagulation | 82.8% (901) | 82.6% (580) | 83.2% (312) | 0.87 |
| Absolute contraindication | 6.6% (72) | 6.1% (43) | 7.5% (29) | 0.06 |
| Relative contraindication | 34.1% (371) | 34.6% (243) | 33.2% (128) | 0.06 |
| Known bleeding risk | 42.1% (458) | 41.9% (294) | 42.5% (164) | 0.06 |

P-values compare males and female.

CHA2DS2-VASc: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category.

HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history of predisposition, labile INR, elderly, drugs or alcohol.
Older age and lower ejection fraction – known as independent predictors of bleeding– potentially explain the higher risk of bleeding [17,18]. In the setting of ST-elevation acute myocardial infarction, primary PCI is associated with higher short-term mortality in female patients, possibly attributable to an intrinsic female gender-related unfavorable risk profile [22,23]. Similarly, in the setting of TAVI life-threatening bleedings have been shown to be more frequent in female patients, even if long-term outcomes do not show significant gender difference [8,9]. In the present paper we aimed at assessing whether the gender-based differences observed in PCI and TAVI extend to the LAAO procedure. We found that women do not show a significant difference in terms of technical or procedural success compared to men. The most likely explanation might reside in that the LAAO procedure itself has been methodologically standardized over time. Pre-procedural imaging, either by TEE or increasingly cardiac CT, allows for an accurate assessment of optimal transseptal puncture location and LAA size and morphology to plan the procedure and select the correct device for the specific patient. Over the last decade, increasing operator experience and streamlining of intra-procedural multimodal imaging, both echocardiographic and fluoroscopic, have reduced the rate of procedural failure or adverse events. Of note, all operators participating in the Amplatzer Amulet Observational Study were experienced in the LAAO procedure. This also explains the low rate of periprocedural complications, and especially bleeding, also taking into consideration that, as opposed to PCI or TAVI, LAAO does not require arterial vascular access, known to pose a higher bleeding risk compared to venous access.

### Table 2

| Periprocedural characteristics and outcomes. | All Enrolled (n = 1088) | Male (n = 702) | Female (n = 386) | p-value |
|---------------------------------------------|------------------------|----------------|------------------|--------|
| Procedure duration (minutes)                | 33.4 ± 22.7            | 34.0 ± 23.4     | 32.3 ± 21.3      | 0.31 |
| Total heparin (units)                        | 7499.4 ± 3383.9        | 7839.2 ± 3800.6 | 6882.3 ± 2333.6 | <0.0001 |
| Max ACT (seconds)                            | 291.7 ± 102.4          | 291.4 ± 97.7    | 292.5 ± 111.1    | 0.69 |
| Total contrast (ml)                          | 102.0 ± 80.8           | 105.6 ± 83.6    | 95.3 ± 74.9      | 0.03 |
| Total fluoroscopic time (minutes)            | 13.2 ± 11.3            | 13.1 ± 11.2     | 13.3 ± 11.4      | 0.76 |
| Echo/anesthesia modality                     |                        |                |                  |      |
| TEE & GA                                    | 56.3% (607)            | 58.1% (406)     | 52.9% (201)      | 0.21 |
| TEE & CS                                    | 31.7% (342)            | 30.8% (215)     | 33.4% (127)      |      |
| ICE                                         | 12.1% (130)            | 11.2% (78)      | 13.7% (52)       |      |
| Technical implant success                    | 99.1% (1078)           | 98.9% (694)     | 99.5% (384)      | 0.51 |
| Procedural success (technical success w/o MAE prior to discharge) | 95.5% (1039) | 95.4% (670) | 95.6% (369) | 1.00 |
| Peri-device residual flow                    |                        |                |                  |      |
| < 3 mm                                      | 99.3% (560)            | 99.2% (372)     | 99.5% (188)      | 1.00 |
| ≤ 5 mm                                      | 100% (564)             | 100% (375)      | 100% (189)       | 1.00 |
| Major AEs ≤ 7d                              | 4.0% (44)              | 3.8% (27)       | 4.4% (17)        | 0.63 |
| Death                                       | 0.3% (3)               | 0.1% (1)        | 0.5% (2)         | 0.29 |
| Stroke                                      | 0.4% (4)               | 0.1% (1)        | 0.8% (3)         | 0.13 |
| Systemic embolism                           | 0.0% (0)               | 0.0% (0)        | 0.0% (0)         | 1.00 |
| Major bleed                                 | 2.8% (30)              | 2.6% (18)       | 3.1% (12)        | 0.70 |
| Device embolization                         | 0.2% (2)               | 0.3% (2)        | 0.0% (0)         | 0.54 |
| Major vascular complication                 | 1.3% (14)              | 1.3% (9)        | 1.3% (5)         | 1.00 |
| Procedure-/Device-related SAE ≤ 7 days      | 5.8% (63)              | 5.4% (38)       | 6.5% (25)        | 0.50 |
| Length of stay (days)                       | 2.4 ± 4.0              | 2.1 ± 2.7       | 3.0 ± 5.5        | 0.03 |

P-values compare males and female.
ACT: activated clotting time.
TEE: transesophageal echocardiography.
GA: general anesthesia.
CS: conscious sedation.
ICE: intracardiac echocardiography.
MAE: major adverse event.
SAE: serious adverse event.

![Fig. 1. The antithrombotic medication regimen prescribed over 2 years post-LAAO was comparable between males and females. The majority of patients were discharged on DAPT and transitioned to SAPT at the 1–3 month follow-up visit. At 2 years, >80% of each gender were on SAPT or no antithrombotic medications.](image-url)
4.2. Long term clinical outcomes

Both men and women received similar antithrombotic therapy over time, with almost two thirds of patients in each group discharged on DAPT and almost one quarter on SAPT. The majority of patients assumed a SAPT only regimen one-to-three months after LAAO. We found no gender difference in terms of the composite primary endpoint, nor in the individual endpoints of all-cause mortality, CV mortality, ischemic stroke, TIA, or major bleeding.

Women are at higher thromboembolic risk than men, especially when CHA2DS2-VASc scores ≥ 2, thus explaining why female gender accounts for 1 point [3]. However, given the similar adequateness of anticoagulation, women with AF show a greater thromboembolic risk reduction compared to men, leading to a similar long-term risk of stroke or systemic embolism. Our data in patients undergoing LAAO show similar findings. Despite a higher CHA2DS2-VASc predicted rate in women than men (7.6 vs 6.2%/year), we found a similar rate of ischemic stroke at 2-year follow-up (2.1% for women and 2.2% for men), thus suggesting that, similarly to oral anticoagulation, device-based LAA occlusion renders AF-related stroke risk similar in women and men. Of note, the rate of DRT did not show any gender-related difference. This findings imply that, similar to anticoagulant therapy, device-based mechanical LAA occlusion appears to confer a greater stroke risk reduction in women than men, with no increased risk of DRT.

With regard to bleeding risk, the 2-year follow up rate of major bleedings did not statistically differ between men and women, although compared to HAS-BLED predicted bleeding rate we observed a 3% increase in major bleeding in men (from predicted 6.9% to observed 7.1%) and a 15% increase in women (from predicted 6.6% to observed 7.6%). However, this comparison includes procedure-related bleeding events and may not accurately assess the post-procedure long-term risk for bleeding in females after LAAO. Additionally, given that the HAS-BLED score is calculated for patients taking oral anticoagulation, the absence of bleeding risk

| Table 3 | Discharge Anticoagulation Regimens. |
|---------|------------------------------------|
|         | All Enrolled (n = 1074) | Male (n = 692) | Female (n = 382) |
| OAC without antiplatelets | 4.6% (49) | 4.2% (29) | 5.2% (20) |
| VKA | 1.7% (18) | 1.3% (9) | 2.4% (9) |
| NOAC | 2.9% (31) | 2.9% (20) | 2.9% (11) |
| OAC with antiplatelets | 6.6% (71) | 6.6% (46) | 6.5% (25) |
| VKA | 2.4% (26) | 2.6% (18) | 2.1% (8) |
| NOAC | 4.2% (45) | 4.0% (28) | 4.5% (17) |
| Injectable (e.g., LMWH) | 6.6% (71) | 6.2% (43) | 7.3% (28) |

Note: Discharge medication information available for 1074 subjects (692/702 males and 382/386 females).

OAC: oral anticoagulation.
VKA: vitamin K antagonist.
NOAC: non-vitamin K antagonist.
LMWH: low molecular weight heparin.

| Table 4 | Long term clinical outcomes. |
|---------|------------------------------|
|         | All Enrolled (n = 1088) | Male (n = 702) | Female (n = 386) | p-value |
| Ischemic stroke, systemic embolism, or CV mortality at 2 years | 12.2% (1 2 2) | 12.0% (77) | 12.5% (45) | 0.82 |
| CV mortality at 2 years | 9.9% (90) | 9.0% (58) | 9.0% (32) | 0.91 |
| All-cause mortality at 2 years | 15.2% (157) | 15.6% (104) | 14.5% (53) | 0.53 |
| Ischemic stroke rate | 2.2%/year | 2.2%/year | 2.1%/year | 0.95 |
| Device-related thrombus at 2 years | 1.6% (17) | 1.6% (11) | 1.6% (6) | 0.96 |
| Major bleeding (BARC ≥ 3) | 7.2%/year | 7.1%/year | 7.6%/year | 0.69 |

P-values compare males and female.
CV: cardiovascular.
BARC: Bleeding Academic Research Consortium.

Fig. 2. Clinical outcomes were reported through a 2 year post-LAAO visit and adjudicated by an independent clinical events committee. The primary outcome, a composite of ischemic stroke, systemic embolism, or cardiovascular mortality was similar between genders (A). The rates of cardiovascular mortality (B) and all-cause mortality (C) were also no different between genders over 2 years post-LAAO.
reduction in patients after LAAO might reflect the fact that post-
LAAO antithrombotic therapy was not withdrawn in this population
at very high-risk of bleeding (72% with prior major bleeding),
with around 10% still discharged on anticoagulants and most
patients maintaining SAPT after one year follow-up.

5. Limitations

This sub-analysis was not pre-specified and the Amulet Ovs-
ervational Study was not powered to detect differences in clinical
outcomes between genders. The majority of patients studied were
contraindicated to OAC and only the Amplatzer Amulet device was
utilized. The clinical results reported may not apply to patients
receiving other LAAO devices or receiving LAAO despite tolerating
long-term OAC.

6. Conclusions

In this large group of patients undergoing LAAO using the
Amplatzer™ Amulet™ device we found no significant gender differ-
ence in terms of clinical indication, procedural and long-term out-
come, as opposed to what is usually observed in the setting of
percutaneous coronary or valvular interventions. However, similar
to anticoagulant therapy, device-based mechanical LAA exclusion
renders AF-related stroke risk similar in women and men, with
no increased risk of DRT.

Declaration of Competing Interest

The authors declare that they have no known competing finan-
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to influence the work reported in this paper.

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Dr. Nielsen-Kudsk has served as a proctor and consultant for
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Fig. 3. The observed annualized ischemic stroke rate was similar between males and females (2.2 vs 2.1%/year). Due to higher baseline CHA2DS2-VASc score, and thus increased predicted rate of ischemic stroke, females exhibited greater absolute and relative reductions in ischemic stroke risk, as compared to the predicted rate.
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