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1 **Thoracoscopic Left Atrial Appendage Clipping: a multicenter cohort analysis**

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5 **Short Title: Left atrial appendage clipping**

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28 **Abstract**

29

30 **Objectives:** To document the closure rate, safety and stroke rate after thoracoscopic left atrial
31 appendage (LAA) clipping.

32 **Background:** The LAA is the main source of stroke in patients with AF and thoracoscopic clipping
33 may provide a durable and safe closure technique.

34 **Methods:** We studied consecutive patients undergoing clipping as part of a thoracoscopic maze
35 procedure in 4 referral centers (Netherlands and USA; 2012-2016). Completeness of LAA closure was
36 assessed by either computed tomography (n=100) or transesophageal echocardiography (n=122).
37 The primary outcome was complete LAA closure (absence of residual LAA flow and pouch <10 mm).
38 Secondary outcomes were 30-day complications; the composite of ischemic stroke, hemorrhagic
39 stroke or transient ischemic attack (TIA); and all-cause mortality.

40 **Results:** 222 Patients were included, with a mean age of 66±9 years and 68.5% male. The mean
41 CHA₂DS₂-VASc score was 2.3±1.0. Complete LAA closure was achieved in 95.0% of patients. There
42 were no intraoperative or clip-related complications and the overall 30-day freedom from any
43 complication was 96.4%. Freedom from cerebrovascular events after surgery was 99.1% after median
44 follow-up of 20 months (interquartile range 14-25; 369 patient-years of follow-up) and overall survival
45 was 98.6%. The observed rate of cerebrovascular events after LAA clipping was low (0.5 per 100-
46 patient-years).

47 **Conclusions:** LAA clipping during thoracoscopic ablation is a feasible and safe technique for closure
48 of the LAA in patients with AF. The lower than expected rate of cerebrovascular events after
49 deployment was likely multifactorial, including not only LAA closure, but also the effect of oral
50 anticoagulation and rhythm control.

51

52 **Keywords:** atrial fibrillation; left atrial appendage; left atrial appendage closure; thoracoscopic; stroke;
53 outcomes

54

55 **Condensed Abstract (100 words)**

56 Our objective was to provide cardiologists, surgeons and the multidisciplinary atrial fibrillation (AF)
57 team with adequate information about thoracoscopic left atrial appendage (LAA) clipping in order to
58 make appropriate decisions on stroke prevention. We studied 222 consecutive patients undergoing
59 clipping as part of a thoracoscopic ablation procedure (TT-maze) in 4 referral centers. We observed
60 high LAA closure rates (95.0%) without clip related complications, high overall 30-day freedom from
61 any complication (96.4%) and a low stroke rate (0.5 per 100-patient-years). This suggest that
62 thoracoscopic LAA clipping is a feasible and safe technique for closure of the LAA in patients with AF.

63

64 **Abbreviations**

65 AF: atrial fibrillation

66 CT: computed tomography

67 LA: Left atrium/left atrial

68 LAA: left atrial appendage

69 NOAC: non-vitamin-K-dependent oral anticoagulants

70 TEE: transesophageal echocardiography

71 TIA: transient ischemic attack

72 TT-Maze: totally thoracoscopic maze

73

74 **Introduction**

75 Atrial fibrillation (AF) is a common condition with a prevalence around 3% in adults which is expected
76 to rapidly increase in the next few decades.¹⁻³ AF is an independent risk factor for stroke and rates are
77 three to five-fold higher compared to the general population.¹⁻³ The left atrial appendage (LAA) is
78 thought to be the main source of stroke and emboli in AF patients and hence a variety of techniques
79 have been developed to occlude or close this structure. Various surgical techniques have been
80 described, such as suture ligation, stapling and surgical excision. However, these techniques often
81 result in incomplete occlusion or residual pouches of the LAA that may contribute to thrombus
82 formation and ongoing risk of stroke.^{4,5,6}

83

84 A few small studies have shown promising results of LAA closure by using a clip during either open-
85 heart surgery⁷ or thoracoscopic surgery.^{8,9} In some centers, LAA clipping is routinely performed in
86 combination with thoracoscopic AF ablation as part of the totally thoracoscopic maze procedure (TT-
87 maze).^{10,11} However, we currently lack systematic data about the efficacy of this procedure in terms of
88 successful closure rates, or the safety of this approach. In this multicenter study, we evaluated both
89 procedural success and complications of thoracoscopic clipping in consecutive patients undergoing
90 either TT-maze or hybrid endocardial and epicardial ablation. The purpose of the study was to provide
91 cardiologists, surgeons and the multidisciplinary AF care team with adequate information about this
92 new technique. We hypothesize that thoracoscopic clipping would be an effective and durable
93 approach for closure of the LAA.

94

95 **Methods**

96 This study has a prospective observational cohort design and was approved by the local ethical
97 committee at the St. Antonius Hospital, Nieuwegein, the Catharina Hospital, Eindhoven, St. Helena
98 Hospital, St. Helena and Sutter Medical Center, Sacramento (reference number: W15.077).

99

100 *Patient selection*

101 Consecutive patients who underwent thoracoscopic LAA clipping between February 2012 and March
102 2016 in 4 major referral centers in the Netherlands and USA were included. All patients were suffering
103 from symptomatic, drug-refractory AF and were discussed by the multidisciplinary AF care team (the
104 AF Heart Team) consisting of dedicated cardiac surgeons and electrophysiologists.

105

106 *Study endpoints*

107 The primary outcome for this study was complete LAA closure defined as absence of residual flow in
108 the LAA after clipping, combined with a residual LAA pouch of less than 10 mm revealed by either
109 computed tomography (CT) or transesophageal echocardiography (TEE). CT and TEE were
110 performed in all patients according to local operating procedures, approximately 6 months after
111 surgery (some patients earlier or later depending on clinical need). Complete LAA closure also implied
112 successful introduction of the clip into the chest cavity, positioning and release of the clip and removal
113 of the steering tool.

114 The secondary outcomes were: (1) 30-day freedom from complications; (2) freedom from the
115 combined clinical endpoint of ischemic stroke, hemorrhagic stroke or transient ischemic attack (TIA);
116 and (3) all-cause mortality. The following operative complications were classified as clip related: signs
117 of cardiac ischemia and bleeding related to the introduction of the clip into the chest cavity, clip
118 positioning and release, and conversion to (mini)thoracotomy or sternotomy.

119

120 *Data collection*

121 All patient data were prospectively gathered as each patient went through their surgery and hospital
122 admission; we used medical and operative charts and records, including data on complications
123 (surgical, bleeding and others) and medication usage (including prescription charts for anticoagulation
124 and antiarrhythmic drug therapy).

125 Complications after surgery were extracted from these records using a standardized list of potential
126 complications.¹¹ When patients were referred from other centers, these centers were contacted to
127 assess if any complications from the standardized list occurred between discharge from our hospital
128 and 30 days postoperatively. Survival data were obtained from hospital and national registry data.
129 Stroke data and medication history at latest follow-up were obtained by telephone interviews with all
130 individual patients. Patients were interviewed according to the Questionnaire for Verifying Stroke-Free
131 Status.¹² Additionally we contacted the neurologists at local hospitals to check for confirmation of any
132 diagnosis of a cerebrovascular event. Neurologic events in this series were confirmed by MRI-scan
133 according to local clinical protocols.

134

135 *Device*

136 Details of the clip (AtriClip™, AtriCure, Inc. Mason, Ohio, USA) have been described previously.¹³ In
137 brief, the clip is composed of two parallel titanium crossbars covered with a woven polyester sheath.
138 Nitinol springs at each end provides, dynamic, parallel pressure on the tissue causing tissue necrosis.
139 The clip can be easily repositioned prior to being deployed if required.

140

141 *Surgical Procedure*

142 An extensive and video-guided description of the TT-maze has been published previously.¹⁰ In brief,
143 the TT-maze consists of an epicardial pulmonary vein isolation with creation of a box through bilateral
144 video-assisted thoracoscopic surgery using the AtriCure Isolator Synergy ablation clamp (AtriCure Inc)
145 and the Cool rail pen (AtriCure Inc). The box is connected with the base of the LAA and furthermore
146 with the left fibrous trigone. The endpoint of the ablation is sinus rhythm and bidirectional block
147 confirmation of the pulmonary veins and box. Clipping of the LAA is performed in all patients
148 immediately after ablation as a routine part of the TT-maze procedure. First, the length of the base of
149 the LAA is measured with a sizer. The appropriate clip is then introduced and directed parallel to the
150 base of the LAA. The clip is opened and manipulated over the LAA assisted by a blunt suction device.
151 The clip is then closed after direct thoracoscopic confirmation of correct positioning fully against the
152 LAA base. The clip is opened and repositioned in case of a suboptimal position and/or a residual
153 pouch revealed by TEE or by direct thoracoscopic view. After conformation of an appropriate position

154 of the clip, release of the clip from the steering tool is delayed for 30 seconds to rule out
155 electrocardiographic ST-segment changes and wall motion disturbances on TEE.

156

157 *Postoperative care and follow-up*

158 Oral anticoagulation was initiated on the first postoperative day with either non-vitamin-K-dependent
159 oral anticoagulants (NOAC), or vitamin-K-antagonists and low-molecular-weight heparin injections
160 until an International Normalized Ratio level of ≥ 2 was achieved. The next day, anti-arrhythmic drugs
161 were restarted depending on heart rate and rhythm. After discharge management of oral
162 anticoagulation and anti-arrhythmic drugs were left to the discretion of the referring cardiologist.

163

164 *Computed tomography-scan*

165 CT-scans were performed according to the local protocol. A dual-source CT scanner system, 256-or
166 356-slice CT scanner with non-ionic contrast medium was used. Three-dimensional reconstructions
167 were created. The base of the LAA was defined as the line that starts 3 mm peripheral from the
168 circumflex vein or artery on the coronal sections. From this point, an imaginary line is directed towards
169 the sharp angle representing the border between the LAA and the epicardium. The distance between
170 the mid part of this imaginary line and the clip, was systematically measured and defined as residual
171 pouch length (Figure 1). All CT-scans were adjudicated by an independent radiologist (HWVE).

172

173 *Transesophageal echocardiography*

174 TEE imaging of the LAA was systematically performed by an independent cardiologist according to the
175 local protocol. Starting with the high mid-oesophageal view at 0 degrees, followed by views at 45, 60,
176 90 and 105 degrees from the top of the mitral valve annulus, with further views as necessary for
177 optimal imaging, including a 3D and en-face view of the LAA orifice.

178

179 *Statistics*

180 Descriptive statistics were used to report patients' characteristics. Continuous variables were reported
181 as mean \pm standard deviation. Percentages were used to report categorical variables. The estimated
182 event-free survival probabilities were calculated using Kaplan–Meier analysis. Data were analyzed
183 using SPSS version 22 and Stata version 14.2.

184

186 **Results**

187

188 *Patient characteristics*

189 Patient characteristics are outlined in Table 1. In total 222 patients were included in our analysis: St.
190 Antonius Hospital (n=67, 2 operating surgeons), the Catharina Hospital (n=33, 1 operating surgeon),
191 St. Helena Hospital (n=66, 1 operating surgeon) and Sutter Medical Center (n=56, 1 operating
192 surgeon). 70.3% (n=156) underwent thoracoscopic LAA clipping as part of a standalone TT-maze and
193 29.7% (n=66) as part of thoracoscopic procedure followed by a planned second stage catheter
194 ablation (hybrid maze procedure including epicardial then endocardial ablation after 6 weeks).
195 The mean age of the patients was 66±9 years and 68.5% (n=152) were male. Paroxysmal AF was
196 present in 17.3% (n=38), persistent AF in 28.6% (n=63), longstanding persistent in 52.7% (n=116) and
197 atypical atrial flutter in 1.4% (n=3). Mean arrhythmia duration prior to surgery was 8±8 years. Previous
198 catheter ablation was performed in 45.5% (n=101) and a documented prior history of ischemic stroke
199 was reported in 9.9% (n=22). Mild or moderate mitral regurgitation was present in 36.6% (n=81) and
200 left ventricular ejection fraction < 50% in 23.5% (n=52). The mean CHA₂DS₂-VASc score was 2.3±1.5,
201 the mean CHADS₂ score was 1.3±1.1 and the median hospital stay was 4 days (interquartile range 3-
202 6 days). No patients were lost to follow-up.

203

204 *Primary outcome*

205 Complete closure was achieved in 95.0% (211/222) as assessed with CT-scan or TEE after a median
206 period of 6 months after the LAA clipping procedure (interquartile range 3-8 months).

207 In those with a follow-up CT-scan, complete closure of the LAA was obtained in 93.0% (93/100).

208 Absence of residual flow or contrast peripheral to the clip was confirmed in all patients. A residual
209 pouch of more than 10 mm was present in 7 patients and the overall mean size of the residual pouch
210 was 14±3 mm [range: 11-19 mm]. In 2 patients a residual pouch could not be measured because of
211 poor quality of the CT-scan. In 1 patient the LAA was clipped partially and repositioning was not
212 possible. Therefore a second clip was introduced and positioned over the first clip into an adequate
213 position at the base of the LAA.

214 In those patients with a follow-up TEE, complete closure of the LAA was obtained in 96.7% (118/122).

215 Absence of residual flow peripheral to the clip was confirmed in all patients. A residual pouch of more

216 than 10 mm was observed in 4 patients and the overall mean size of the pouch was 16±5 mm [range:
217 10-21 mm].

218

219 *Secondary outcomes*

220 Surgical complications: No intraoperative complications occurred and there were no clip-related
221 complications seen. No patients died during 30-day follow-up. Overall freedom from any 30-day
222 complication was 96.4%. All complications that occurred are listed in Tables 2 and 3. The 30-day
223 major complication rate was 0.9% (n=2) and minor complication rate was 4.5% (n=10).

224 Cerebrovascular events: The freedom from the combined endpoint of ischemic stroke, hemorrhagic
225 stroke or TIA was 99.1% over 369 patient-years of follow-up (median length of follow-up 20 months;
226 interquartile range 14-25 months); Figure 2A. The observed cerebrovascular event rate was low at 0.5
227 per 100 patient-years, with 57% of patients not on oral anticoagulation therapy at latest follow-up. In
228 detail, one patient had an ischemic stroke confirmed on MRI 24 months after TT-maze (CHA₂DS₂-
229 VASc score 3, on oral anticoagulation therapy and in sinus rhythm at the time), and another patient
230 had a TIA 30 months after TT-maze (CHA₂DS₂-VASc score 1 and off oral anticoagulation therapy).
231 All-cause mortality: 3 patients died during median follow-up of 14 months (interquartile range 9-22
232 months), all of non-cardiac causes; Figure 2B.

233

234

235 **Discussion**

236 Stroke prevention is one of the cornerstones of AF treatment. The LAA is the main source of thrombo-
237 embolism in AF patients, due to blood stasis and coagulation, fulfilling the main conditions of
238 Virchow's triad.¹⁴⁻¹⁸ Oral anticoagulation is the mainstay of stroke prevention in AF, but other
239 strategies are now available and can complement interventional approaches to rhythm control. This is
240 the first observational multicenter cohort study evaluating procedural success and complications of
241 thoracoscopic LAA clipping. We observed high LAA closure rates (95.0%), the absence of clip related
242 complications, and a low rate of cerebrovascular events at 0.5 per 100 patient years. To put into
243 context for a CHA₂DS₂-VASc score of 2 in large population databases, the event rate in non-
244 anticoagulated patients is approximately 2.0 per 100 patient years, 1.2 per 100 patient years for those
245 with a similar rate of anticoagulation as observed in our cohort, and 0.7 per 100 patient years for those
246 fully anticoagulated (Table 4).¹⁹⁻²²

247

248 *Surgical LAA closure*

249 Various surgical techniques of LAA closure have been described, such as suture ligation, stapling and
250 surgical excision. These techniques are associated with incomplete LAA closure rates of 40-60%.^{5,6}
251 Depending on the morphology after incomplete closure, these remnant LAA may present an ongoing
252 risk of thrombus formation and embolisation.^{23,24} Our data on LAA clipping have shown a complete
253 closure rate of 95.0% based on a large cohort of consecutive patients in 4 different referral centers,
254 consistent with published data from a smaller single center cohort.²⁵ Put together, these data suggest
255 that thoracoscopic LAA clipping has overcome the problems of reproducibility seen in other surgical
256 techniques. Interestingly, long-term follow-up data from LAA clipping in patients undergoing
257 sternotomy showed stable closure rates of 100% after 5 years.⁷ We speculate that the closure rate in
258 our patient group will also remain stable, since the clips used in our study were similar.
259 The primary outcome in this study, complete closure rate, depends on the applied definition of
260 complete closure. Earlier papers from LAA clipping randomly used a cut-off value of 10 mm for the
261 definition of complete closure without a clear anatomic description of how the LAA pouch was
262 assessed.^{9,26,27} We therefore decided to accept the fairly liberal cut-off point of 10 mm as the second
263 condition for the definition of complete closure. Absence of any contrast peripherally from the clip in all

264 patients in this series seems to be a beneficial difference compared to significant (≥ 3 -5 mm) or not-
265 significant (≤ 3 -5 mm) peridevice leaks described for the percutaneous closure devices.

266

267 *Percutaneous transcatheter LAA occlusion*

268 Percutaneous transcatheter LAA occlusion, including the WATCHMAN device (Boston Scientific Inc,
269 Marlborough, USA) the Amplatzer (St. Jude Medical, Minneapolis, USA) and the Lariat LAA exclusion
270 system (SentreHeart Inc, Redwood City, California, USA) are associated with closure rates varying
271 from 91-98.5%.²⁸⁻³⁴ However, the definition of success included peri-device leakage of ≤ 3 -5 mm in
272 diameter for WATCHMAN and Amplatzer (8-13% of the patients^{30,31,33}) and 2 mm in diameter for
273 Lariat (n=13, 1.8%).³⁴ Although these remnant orifices are small, the clinical relevance is unknown and
274 might possibly explain why the overall stroke rate after 5 years is non-inferior to warfarin therapy only.
275 No comparison studies between percutaneous LAA closure and NOAC therapy are as yet available.
276 Another potential challenge of percutaneous devices is the risk of device related thrombus.³³
277 The event rate for the composite endpoint of stroke and systemic embolism was 1.0% (mean CHADS₂
278 score 2.4) and 1.6% (mean CHADS₂ score 2.2) per year for Lariat (SentreHeart Inc) and WATCHMAN
279 (Boston Scientific Inc) respectively.^{35,36}

280 Although the 30-day complication rate in our study (5.4%) was not directly clip related, it is in line with
281 the device related complication rates described after percutaneous devices (8.7%) and Lariat
282 implantation (5.3%).^{29,36,37} The recently published EWOLUTION trial showed a 30-day device and
283 procedure-related complication rate of 3.6%, indicating a learning-curve effect for percutaneous
284 devices,³³ which is also likely to apply to thoracoscopic LAA clipping. In contrast to the WATCHMAN,
285 Amplatzer and Lariat system which are all restricted to ostial size, LAA size or morphology,
286 thoracoscopic LAA clipping is performed under direct view irrespective of LAA size, anatomy or atrial
287 dilatation.

288

289 *Current guidelines*

290 Current guidelines suggest continuation of anticoagulation therapy in patients at risk for stroke after
291 closure or exclusion of the LAA, even after successful ablation.¹ This can be explained by several
292 reasons: that successful ablation does not guarantee maintenance of sinus rhythm, (recurrent) AF is
293 often asymptomatic, and that the LAA is not the only source of stroke. Adequately powered

294 randomized controlled trials investigating the effect of LAA closure on stroke reduction are not
295 available,³⁸ and we await results from the Left Atrial Appendage Occlusion Study III (LAAOS III)
296 comparing cardiac surgery with and without LAA closure in AF patients. However, many clinicians
297 tend to stop anticoagulation therapy after successful ablation and/or closure or exclusion of the LAA
298 despite elevated stroke risk. This approach can only be condoned after appropriate trials have
299 demonstrated safety, in particular the comparison between LAA closure/exclusion and NOAC therapy.
300 Even with anticoagulation, there is a residual risk of stroke in patients with AF that should be
301 considered and discussed with patients.^{1,39}

302

303 *Limitations*

304 Although this is the first multicenter study reporting on the efficacy and safety of LAA clipping, it is an
305 observational study with potential risk of selection bias. As described in our methods section, patients
306 eligible for TT-maze were first discussed and referred by the multidisciplinary AF care team. They are
307 not representative of an “average” AF population since 46% had prior catheter ablation. Furthermore,
308 the low event rate of cerebrovascular events was likely multifactorial including not only the LAA clip,
309 but also the effect of oral anticoagulation and rhythm control. Although we report on the number of
310 patients taking anticoagulation at the end of follow-up, periods on and off anticoagulation, and the time
311 in therapeutic range for those on vitamin-K-antagonists, was not collected. The follow-up time was
312 relatively short and patient numbers limited, and therefore no definite conclusions regarding stroke
313 reduction can be made. Although we provide a detailed overview of 30-day complications, long-term
314 events (aside from cerebrovascular events and mortality) were not studied.

315

316 **Conclusion**

317 Thoracoscopic LAA clipping is a feasible and safe LAA closure approach with lower than expected
318 rates of stroke after deployment. Randomized trials are required to directly compare this approach
319 with and without cessation of NOAC therapy to assess the place of thoracoscopic LAA clipping for
320 stroke prevention in AF.

321

322

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447

448

449 **Table 1. Patient characteristics**

Results	Total N=222
Age, years	66±9
Male gender	152 (68.5%)
Mean duration of AF, years	8±8
Type of AF	
Paroxysmal AF	38 (17.3%)
Persistent AF	63 (28.6%)
Longstanding persistent AF	116 (52.7%)
Atrial flutter	3 (1.4%)
Left ventricular ejection fraction	
> 50%	169 (76.5%)
< 50%	52 (23.5%)
Mitral regurgitation	
None	65 (29.4%)
Trace	74 (33.5%)
Mild	61 (27.6%)
Moderate	20 (9.0%)
Moderately severe	1 (0.5%)
CHA ₂ DS ₂ -VASc score	2.3±1
CHADS ₂ score	1.2±1
Prior catheter ablation	100 (45.5%)
Of which > 1 procedure	63 (28.8%)
History of ischemic stroke	22 (9.9%)

452 **Table 2. Intraoperative complications**

453

Complication	N (%)
Mortality	0 (0.0)
Stroke	0 (0.0)
Sternotomy for bleeding	0 (0.0)
Mini-sternotomy for bleeding	0 (0.0)
Mini-thoracotomy for bleeding	0 (0.0)
Bleeding with discontinuation of procedure	0 (0.0)
Total number of intraoperative complications, n (%)	0 (0.0)

454

455 Standardized reporting of intraoperative complications is presented according to published criteria.⁴⁰

456

457 **Table 3. Postoperative complications**

Major	N (%)
Clip related complications	0 (0.0)
Death	0 (0.0)
Reinterventions*:	
Hemothorax	0 (0.0)
Pericardial effusion/tamponade	0 (0.0)
Empyema	1 (0.5)
Re-intubation to hemodynamic instability	1 (0.5)
Re-intubation without hemodynamic instability	0 (0.0)
Venous lung Infarction	0 (0.0)
Lung emboli	0 (0.0)
Permanent phrenic nerve paralysis	0 (0.0)
Stroke	0 (0.0)
Transient Ischemic Attack	0 (0.0)
Atrium-esophagus fistula	0 (0.0)
Myocardial infarction	0 (0.0)
Total number of patients with ≥ 1 major complication	2 (0.9)
Total number of major complications	2 (0.9)
Minor	
Pericardial fluid necessitating pericardiocentesis	0 (0.0)
Permanent pacemaker implantation	2 (0.9)
Thoracostomy drain for:	
Pneumothorax	0 (0.0)

Pleural effusion	3 (1.4)
Hemothorax	1 (0.5)
Infections:	
Airway infection	1 (0.5)
Urinary tract infection	2 (0.9)
Superficial wound infection	0 (0.0)
Delirium	1 (0.5)
Gastrointestinal bleeding	0 (0.0)
Total number of patients with ≥ 1 minor complication	8 (3.6)
Total number of minor complications	10 (4.5)
Overall freedom from 30-day complications	96.4%

458

459 Standardized reporting of postoperative complications is presented according to published criteria.⁴⁰

460 †Including thoracotomy, sternotomy or Video-Assisted-Thoracoscopic Surgery.

461

462 **Table 4: Indirect comparison of events with a CHA₂DS₂-VASc score of 2**

Study	Oral anticoagulation use (%)	CHA ₂ DS ₂ -VASc	Outcome	Person-years of follow-up	Rate per 100 person-years	Description study
Nielsen ²¹	0%	2	Ischemic stroke and systemic embolism	114,034	2.0	Danish nationwide observational study of hospitalized AF patients not receiving anticoagulation
Van de Ham ²²	0%	2	Ischemic stroke	21,500	1.9	UK observational general practice electronic health record database of AF patients not receiving anticoagulation
Allen et al ²⁰	43%	2	Ischemic stroke	37,750	1.2	UK observational general practice electronic health record database of AF patients with and without anticoagulation
THIS STUDY	43%	Mean 2.3	Ischemic stroke and transient ischemic attack	369	0.5	US and Netherlands observational study of patients undergoing LAA clipping during thoracoscopic AF ablation
Yao et al ¹⁹	100%	2 to 3	Ischemic stroke and systemic embolism	26,250	0.7	US commercial insurance database of AF patients initiated on anticoagulation

