The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 3, 2021 VOL. 384 NO. 22

Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke

R.P. Whitlock, E.P. Belley-Cote, D. Paparella, J.S. Healey, K. Brady, M. Sharma, W. Reents, P. Budera, A.J. Baddour, P. Fila, P.J. Devereaux, A. Bogachev-Prokophiev, A. Boening, K.H.T. Teoh, G.I. Tagarakis, M.S. Slaughter, A.G. Royse, S. McGuinness, M. Alings, P.P. Punjabi, C.D. Mazer, R.J. Folkeringa, A. Colli, Á. Avezum, J. Nakamya, K. Balasubramanian, J. Vincent, P. Voisine, A. Lamy, S. Yusuf, and S.J. Connolly, for the LAAOS III Investigators*

ABSTRACT

BACKGROUND

Surgical occlusion of the left atrial appendage has been hypothesized to prevent ischemic stroke in patients with atrial fibrillation, but this has not been proved. The procedure can be performed during cardiac surgery undertaken for other reasons.

METHODS

We conducted a multicenter, randomized trial involving participants with atrial fibrillation and a CHA_2DS_2-VASc score of at least 2 (on a scale from 0 to 9, with higher scores indicating greater risk of stroke) who were scheduled to undergo cardiac surgery for another indication. The participants were randomly assigned to undergo or not undergo occlusion of the left atrial appendage during surgery; all the participants were expected to receive usual care, including oral anticoagulation, during follow-up. The primary outcome was the occurrence of ischemic stroke (including transient ischemic attack with positive neuroimaging) or systemic embolism. The participants, research personnel, and primary care physicians (other than the surgeons) were unaware of the trial-group assignments.

RESULTS

The primary analysis population included 2379 participants in the occlusion group and 2391 in the no-occlusion group, with a mean age of 71 years and a mean CHA_2DS_2-VASc score of 4.2. The participants were followed for a mean of 3.8 years. A total of 92.1% of the participants received the assigned procedure, and at 3 years, 76.8% of the participants continued to receive oral anticoagulation. Stroke or systemic embolism occurred in 114 participants (4.8%) in the occlusion group and in 168 (7.0%) in the no-occlusion group (hazard ratio, 0.67; 95% confidence interval, 0.53 to 0.85; P=0.001). The incidence of perioperative bleeding, heart failure, or death did not differ significantly between the trial groups.

CONCLUSIONS

Among participants with atrial fibrillation who had undergone cardiac surgery, most of whom continued to receive ongoing antithrombotic therapy, the risk of ischemic stroke or systemic embolism was lower with concomitant left atrial appendage occlusion performed during the surgery than without it. (Funded by the Canadian Institutes of Health Research and others; LAAOS III ClinicalTrials.gov number, NCT01561651.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Whitlock at the David Braley Research Institute, Hamilton General Hospital, 237 Barton St. E, Hamilton, ON L8L 2X2, Canada, or at richard.whitlock@phri.ca.

*A full list of the LAAOS III Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 15, 2021, at NEJM.org.

N Engl J Med 2021;384:2081-91.
DOI: 10.1056/NEJMoa2101897

Atrial fibrillation is common in elderly patients[1] and is responsible for approximately a quarter of ischemic strokes,[2,3] many of which are cardioembolic[4] and originate from the left atrial appendage.[5] Oral anticoagulation most likely reduces thrombus formation in the left atrial appendage and has proven efficacy and safety in preventing ischemic stroke in patients with atrial fibrillation. However, oral anticoagulation is limited by nonadherence to prescribed medications, drug discontinuation, underdosing, and, for patients treated with vitamin K antagonists, poor control of the international normalized ratio. Left atrial appendage occlusion is hypothesized to reduce the risk of stroke among patients with atrial fibrillation, but this has not been proved in a randomized trial.

When patients with atrial fibrillation undergo cardiac surgery, concomitant occlusion of the left atrial appendage may be performed as an adjunctive procedure. We hypothesized that concomitant occlusion performed at the time of cardiac surgery would reduce the risk of ischemic stroke among patients with a history of atrial fibrillation receiving usual care, including anticoagulation. If effective, concomitant occlusion would provide protection against ischemic stroke in addition to the protection provided by anticoagulant therapy. Once performed, the effects of the procedure are permanent.

We conducted the Left Atrial Appendage Occlusion Study (LAAOS III) to evaluate the efficacy and safety of concomitant left atrial appendage occlusion in participants with a history of atrial fibrillation undergoing cardiac surgery for another indication. Specifically, we aimed to determine whether concomitant occlusion would prevent ischemic stroke or systemic embolism in participants who continued to receive usual care, including anticoagulation.

Methods

Trial Design and Oversight

LAAOS III was a multicenter, randomized trial that was funded by peer-reviewed funding sources. The Population Health Research Institute was the sponsor, served as the coordinating center, and was responsible for the maintenance of the database, validation and analyses of the data, and trial coordination. The funders had no role in the design or conduct of the trial; the collection, analysis, or interpretation of the data; or the preparation of the manuscript. The trial was designed by the first and last authors, overseen by the steering committee, and carried out by the trial investigators (see the Supplementary Appendix, available with the full text of this article at NEJM.org).[6] The ethics committee at each participating trial site approved the trial. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

Participants

We enrolled patients 18 years of age or older who were scheduled to undergo cardiac surgery with cardiopulmonary bypass and had a history of atrial fibrillation and a score of at least 2 on the CHA_2DS_2-VASc scale. Scores on the CHA_2DS_2-VASc scale reflect the risk of stroke among patients with atrial fibrillation; scores range from 0 to 9, with higher scores indicating greater risk. We excluded patients undergoing off-pump surgery, mechanical-valve implantation, heart transplantation, surgery for complex congenital heart disease, or isolated implantation of a left ventricular assist device; those with a previous surgery that involved opening the pericardium; and those who had previously undergone implantation of a left atrial appendage closure device. Written informed consent was obtained from all the participants before enrollment.

Procedures

The participants were randomly assigned in a 1:1 ratio, with the use of a Web-based randomization system, to undergo or not undergo occlusion of the left atrial appendage at the time of cardiac surgery for another indication. Randomization was performed according to a computer-generated randomization list, stratified according to trial site, with varying block sizes of 2 and 4. The participants, trial personnel, and clinicians caring for the participants (other than the surgeons) were unaware of the trial-group assignments. A confidential email that indicated the assigned procedure for the participant was sent only to the surgeons just before surgery. In a follow-up email 24 hours after randomization, the surgeons provided information on whether

they had complied with performing the assigned procedure, the method used to perform the surgical occlusion, and whether the occlusion was successful. Surgical reports indicated only that participants were enrolled in LAAOS III and may have undergone occlusion of the left atrial appendage. Surgeons and the intraoperative teams were not involved with ongoing management of antithrombotic therapy or further collection of the data.

Left atrial appendage occlusion was performed during cardiac surgery with the use of any of the following techniques: amputation and closure (preferred), stapler closure, double-layer linear closure from within the atrium in participants undergoing minithoracotomy (this approach required transesophageal echocardiographic confirmation of the occlusion), or closure with an approved surgical occlusion device (Fig. S1 in the Supplementary Appendix). Neither percutaneous closure nor purse-string closure was permitted. Intraoperative transesophageal echocardiography was recommended to confirm successful closure. If the initial closure had failed, additional maneuvers were performed immediately to rectify the failure. If a participant had a thrombus identified in the appendage, the left atrium was opened to remove the thrombus before occlusion.

Participants were followed up by telephone or in person (primarily by telephone) by local trial personnel at 30 days and then every 6 months to a common trial end date (the date of the final visit was January 28, 2021). Physicians who oversaw antithrombotic therapy were unaware of trial-group assignments. Participants were expected to receive guideline-directed stroke prevention and other usual care. Trial personnel collected data on anticoagulation use and, if a participant was not receiving oral anticoagulation during follow-up, on the specific reasons for not doing so. Every 6 months, the participants were questioned with the use of a validated stroke questionnaire[7] to determine if symptoms indicating a possible stroke had occurred. If such symptoms were reported, source documentation was obtained. Trial centers reported strokes or systemic emboli with specialized report forms. An adjudication committee consisting of physicians trained in the protocol definitions reviewed all strokes, transient ischemic attacks, and systemic emboli in a blinded manner; all strokes and transient ischemic attacks were reviewed by stroke neurologists.

OUTCOMES

The primary outcome was the first occurrence of ischemic stroke (including transient ischemic attack with positive neuroimaging[8]) or noncerebral systemic embolism during follow-up. Strokes of undetermined cause were included as ischemic strokes in the primary analysis. Secondary outcomes included any stroke or noncerebral systemic embolism; ischemic stroke, noncerebral systemic embolism, or death from any cause; death from any cause; 30-day mortality; the volume of chest-tube drainage in the first 24 hours after surgery; reexploration for bleeding within the first 48 hours after surgery; hospitalization for heart failure; myocardial infarction; and major bleeding.[9] Definitions of trial outcomes are provided in the Supplementary Appendix.

STATISTICAL ANALYSES

The primary hypothesis was that the risk of stroke or systemic embolism would be lower with surgical occlusion of the left atrial appendage added to usual care than with no occlusion added to usual care. Assuming a rate of a primary-outcome event of 2.5% per year in the no-occlusion group and allowing for a rate of crossover of 7% and a rate of loss to follow-up due to nonstroke-related death of 2% per year, we estimated that a sample size of 4700 participants, with a median follow-up of 4 years, would provide the trial 80% power to detect a 25% lower relative risk of a primary-outcome event in the occlusion group than in the no-occlusion group. The estimated rate of a primary-outcome event in the no-occlusion group was based on the assumption that the mean CHA_2DS_2-VASc score would be at least 2.3 and that 65% of the participants would continue to receive anticoagulation (a vitamin K antagonist in 45% and a direct oral anticoagulant in 20%) over the follow-up period.

The primary analysis included all the participants who underwent cardiac surgery. All the participants were followed, irrespective of whether they had undergone surgery, as long as they did not withdraw consent. A time-to-event analysis was used to test the primary hypothesis with the use of Kaplan–Meier survival curves and log-rank testing. The treatment effect was esti-

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline, Antithrombotic Therapy, and Surgical Treatments.*

Variable	Occlusion (N=2379)	No Occlusion (N=2391)
Participants		
Age — yr	71.3±8.4	71.1±8.3
Male sex — no. (%)	1617 (68.0)	1601 (67.0)
Type of atrial fibrillation — no. (%)		
Permanent	692 (29.1)	707 (29.6)
Persistent	577 (24.3)	508 (21.3)
Paroxysmal	1110 (46.7)	1176 (49.2)
Medical history — no. (%)		
Previous myocardial infarction	567 (23.8)	583 (24.4)
Previous stroke	214 (9.0)	219 (9.2)
Rheumatic heart disease	165 (6.9)	162 (6.8)
Peripheral arterial disease	236 (9.9)	256 (10.7)
History of heart failure	1348 (56.7)	1372 (57.4)
Diabetes mellitus	770 (32.4)	765 (32.0)
Aortic plaque	240 (10.1)	231 (9.7)
Smoking, former or current	1127 (47.4)	1173 (49.1)
Hypertension	1960 (82.4)	1941 (81.2)
CHA_2DS_2-VASc score†		
Mean	4.2±1.5	4.2±1.5
Median (interquartile range)	4 (3–5)	4 (3–5)
Atrial fibrillation on baseline ECG — no. (%)	1392 (58.5)	1338 (56.0)
Left ventricular ejection fraction <50% — no./total no. (%)	671/2179 (30.8)	669/2188 (30.6)
Anticoagulant therapy within 7 days before surgery		
Vitamin K antagonist — no. (%)	541 (22.7)	542 (22.7)
Direct oral anticoagulant — no. (%)	674 (28.3)	705 (29.5)
Neither direct oral anticoagulant nor vitamin K antagonist — no. (%)	1164 (48.9)	1144 (47.8)
Cardiac surgery		
Surgical procedure performed — no. (%)		
Isolated CABG	482 (20.3)	522 (21.8)
Isolated valve replacement	552 (23.2)	572 (23.9)
Other	1344 (56.5)	1296 (54.2)
Any valve procedure	1565 (65.8)	1614 (67.5)
Mitral	856 (36.0)	880 (36.8)
Aortic	837 (35.2)	858 (35.9)
Tricuspid	397 (16.7)	427 (17.9)
Pulmonic	2 (0.1)	4 (0.2)
Any aortic procedure	146 (6.1)	134 (5.6)
Concomitant surgical ablation of atrial fibrillation — no. (%)	809 (34.0)	753 (31.5)
Received assigned procedure — no. (%)	2131 (89.6)	2262 (94.6)

Table 1. (Continued.)

Variable	Occlusion (N=2379)	No Occlusion (N=2391)
Left atrial appendage occlusion‡		
Occlusion attempted — no. (%)	2131 (89.6)	NA
Occlusion method — no./total no. (%)§		
Cut and sew	939/1685 (55.7)	NA
Stapler	189/1685 (11.2)	NA
Closure device	255/1685 (15.1)	NA
Closure from within	233/1685 (13.8)	NA
Other approved techniques	69/1685 (4.1)	NA

* Plus–minus values are means ±SD. The participants in the occlusion group underwent left atrial appendage occlusion at the time of cardiac surgery for another indication, and those in the no-occlusion group did not undergo left atrial appendage occlusion at the time of cardiac surgery; all participants were expected to receive usual care. Percentages may not total 100 because of rounding. CABG denotes coronary-artery bypass grafting, ECG electrocardiogram, and NA not applicable.

† Scores on the CHA_2DS_2-VASc scale reflect the risk of stroke among patients with atrial fibrillation; scores range from 0 to 9, with higher scores indicating greater risk.

‡ Illustrations depicting the main approved techniques for left atrial appendage occlusion are provided in Figure S1 in the Supplementary Appendix.

§ Information on the method of left atrial appendage occlusion was collected from the surgeon for 1685 of 2379 patients (70.8%).

mated as a hazard ratio with a 95% confidence interval, which was derived with the use of a Cox proportional-hazards model. The proportional-hazards assumption was tested with the use of a graphical method (Fig. S3). An independent data and safety monitoring board reviewed the unblinded data and performed two prespecified interim analyses of efficacy when 50% and 75% of expected primary-outcome events had occurred. The trial could be stopped if the between-group difference in the incidence of a primary-outcome event was at least 4 standard deviations at the first interim analysis or at least 3 standard deviations at the second. These boundaries needed to be crossed in two consecutive analyses performed at least 3 months apart. Because these boundaries were extreme, we did not adjust the final significance level. We performed a landmark analysis of the primary outcome beyond 30 days. Additional Cox models were used to evaluate interactions between trial-group assignment and subgroups of interest.

RESULTS

PARTICIPANT CHARACTERISTICS

From July 2012 through October 2018, a total of 4811 participants from 105 centers in 27 countries were randomly assigned to undergo (2400 participants) or not undergo (2411 participants) left atrial appendage occlusion at the time of cardiac surgery for another indication. On January 28, 2021, after the second formal interim analysis of efficacy, the data and safety monitoring board recommended that the trial be stopped and the results reported. Final follow-up visits occurred between January 28, 2021, and March 11, 2021. The mean duration of follow-up was 3.8 years, and follow-up was completed by 97.9% of the participants; 50 participants (1.1%) had withdrawn consent and 49 (1.0%) had been lost to follow-up (Fig. S2).

The primary analysis population included 2379 participants in the occlusion group and 2391 in the no-occlusion group. The trial groups were balanced with respect to baseline characteristics (Table 1). The mean age of the participants was 71 years, and 67.5% were men. The mean CHA_2DS_2-VASc score was 4.2, and approximately half the participants were receiving oral anticoagulation at baseline. The median time from randomization to surgery was 0.6 days in both groups. The mean cross-clamp time was 86 minutes in the occlusion group and 82 minutes in the no-occlusion group, and the mean cardiopulmonary bypass time was 119 minutes

Table 2. Trial Outcomes.*

Outcome	Occlusion (N=2379)	No Occlusion (N=2391)	Comparison†
	no. of participants (%)		
Primary			
Ischemic stroke or systemic embolism	114 (4.8)	168 (7.0)	0.67 (0.53 to 0.85)‡
Ischemic stroke	109 (4.6)	164 (6.9)	0.66 (0.52 to 0.84)
Systemic embolism	6 (0.3)	7 (0.3)	0.86 (0.29 to 2.55)
Secondary			
Any stroke or systemic embolism	127 (5.3)	187 (7.8)	0.67 (0.54 to 0.84)
Any stroke	113 (4.7)	176 (7.4)	0.63 (0.50 to 0.80)
Ischemic stroke, systemic embolism, or death from any cause	601 (25.3)	639 (26.7)	0.93 (0.83 to 1.04)
Death from any cause	538 (22.6)	537 (22.5)	1.00 (0.89 to 1.13)
Hospitalization for heart failure§	183 (7.7)	162 (6.8)	1.13 (0.92 to 1.40)
Major bleeding event	248 (10.4)	267 (11.2)	0.93 (0.78 to 1.11)
Myocardial infarction	49 (2.1)	56 (2.3)	0.87 (0.59 to 1.28)
Ischemic stroke or systemic embolism within the first 30 days after surgery	53 (2.2)	65 (2.7)	0.82 (0.57 to 1.18)
Ischemic stroke or systemic embolism beyond 30 days after surgery¶	61 (2.7)	103 (4.6)	0.58 (0.42 to 0.80)
Operative			
Bypass time — min	119±48	113±47	5 (3 to 8)‖
Cross-clamp time — min	86±37	82±37	4 (1 to 6)‖
Median chest-tube output (IQR) — ml	520 (350 to 790)	500 (340 to 760)	20 (–2 to 42)**
Reoperation for bleeding within 48 hours after surgery — no. (%)	94 (4.0)	95 (4.0)	0.99 (0.75 to 1.32)††
Prolongation of index hospitalization due to heart failure — no. (%)	5 (0.2)	14 (0.6)	0.36 (0.13 to 0.99)††
Death within 30 days — no. (%)	89 (3.7)	95 (4.0)	0.94 (0.71 to 1.25)††

* Plus–minus values are means ±SD. All outcomes that do not include death as a component were also analyzed with the use of the Fine and Gray model for competing risk of death, which produced virtually identical effect estimates. Ischemic stroke includes transient ischemic attack with positive neuroimaging and stroke of unknown cause, and any stroke includes definite ischemic stroke, definite hemorrhagic stroke, or uncertain type of stroke.

† All values are hazard ratios with 95% confidence intervals unless otherwise noted. Except in the case of the primary outcome of ischemic stroke or systemic embolism, the widths of the 95% confidence intervals have not been adjusted, and therefore inferences drawn from this interval may not be reproducible.

‡ P=0.001.

§ Hospitalization for heart failure includes new hospitalization and prolongation of index hospitalization.

¶ The category of ischemic stroke or systemic embolism after 30 days includes only participants who did not have an event or ended follow-up before the cutoff at 30 days (2238 participants in the occlusion group and 2242 in the no-occlusion group).

‖ This value is the difference with 95% confidence interval.

** This value is the difference with interquartile range (IQR).

†† This value is the relative risk with 95% confidence interval.

and 113 minutes, respectively (Table 2). The median chest-tube output was 520 ml in the occlusion group and 500 ml in the no-occlusion group. Reexploration for bleeding within the first 48 hours after surgery occurred in 94 participants (4.0%) in the occlusion group and in 95 (4.0%) in the no-occlusion group. The 30-day mortality was 3.7% in the occlusion group and 4.0% in the no-occlusion group.

At hospital discharge, 83.4% of the participants in the occlusion group and 81.0% of those in the no-occlusion group were receiving oral anticoagulation, and the corresponding values were 79.6% and 78.9% at the 1-year visit and

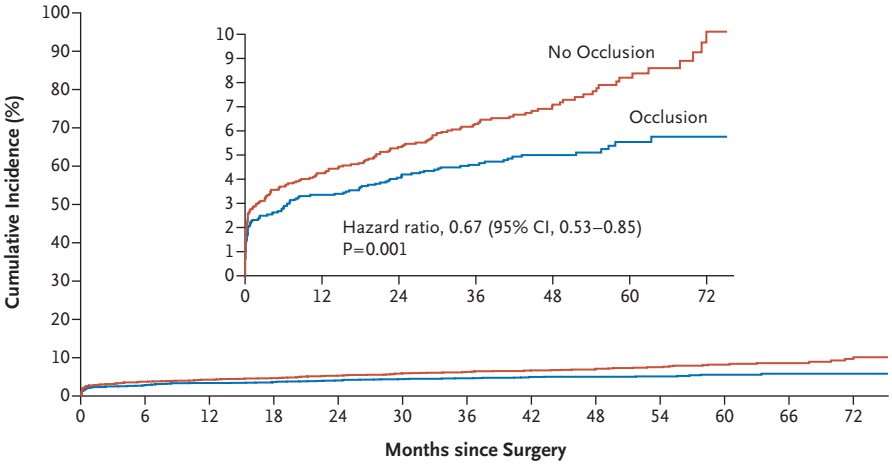

Figure 1. Cumulative Incidence of Stroke or Systemic Arterial Embolism.

The participants in the occlusion group underwent left atrial appendage occlusion at the time of cardiac surgery for another indication, and those in the no-occlusion did not undergo left atrial appendage occlusion at the time of cardiac surgery; all participants were expected to receive usual care. The inset shows the same data on an enlarged y axis.

75.3% and 78.2% at the 3-year visit. More information regarding the use of vitamin K antagonists and direct oral anticoagulants during follow-up is provided in Table S1.

PRIMARY OUTCOME

The validity of the proportional-hazards assumption was assessed with the use of a log–log plot (Fig. S3). Ischemic stroke or systemic embolism occurred in 114 participants (4.8%) in the occlusion group and in 168 (7.0%) in the no-occlusion group (hazard ratio, 0.67; 95% confidence interval [CI], 0.53 to 0.85; P=0.001) (Table 2 and Fig. 1). During the first 30 days after surgery, a primary-outcome event occurred in 53 participants (2.2%) in the occlusion group and in 65 (2.7%) in the no-occlusion group (hazard ratio, 0.82; 95% CI, 0.57 to 1.18). After 30 days, a primary-outcome event occurred in 61 participants (2.7%) in the occlusion group and in 103 (4.6%) in the no-occlusion group (hazard ratio, 0.58; 95% CI, 0.42 to 0.80).

SECONDARY AND SAFETY OUTCOMES

Ischemic stroke occurred in 109 participants (4.6%) in the occlusion group and in 164 (6.9%) in the no-occlusion group (hazard ratio, 0.66; 95% CI, 0.52 to 0.84). Death occurred in 538 participants in the occlusion group (22.6%) and in 537 (22.5%) in the no-occlusion group (hazard ratio, 1.00; 95% CI, 0.89 to 1.13). The cause of death was attributed to stroke in 1.3% of the trial participants (Table S2). Hospitalization for heart failure (either prolongation of index hospitalization or new hospitalization) occurred in 183 participants (7.7%) in the occlusion group and in 162 (6.8%) in the no-occlusion group (hazard ratio, 1.13; 95% CI, 0.92 to 1.40). The incidence of major bleeding or myocardial infarction was similar in the trial groups (Table 2).

ADDITIONAL ANALYSES

The effect of left atrial appendage occlusion on the risk of ischemic stroke or systemic embolism was consistent across subgroups (Fig. 2). The results of the primary-outcome analysis were also consistent with those of the per-protocol, as-treated, and intention-to-treat analyses and with those of the analysis that considered death as a competing risk (Table S3). The intention-to-treat analysis included the participants who did not undergo surgery in addition to those in the primary analysis population.

Subgroup	Occlusion	No Occlusion	Hazard Ratio (95% CI)
	no. of participants with event/total no. (%)		
Sex			
Female	46/762 (6.0)	63/790 (8.0)	0.75 (0.52–1.10)
Male	68/1617 (4.2)	105/1601 (6.6)	0.63 (0.47–0.86)
Age			
<72 yr	40/1075 (3.7)	62/1137 (5.5)	0.67 (0.45–1.00)
≥72 yr	74/1304 (5.7)	106/1254 (8.5)	0.66 (0.49–0.89)
Rheumatic heart disease			
No	110/2214 (5.0)	155/2229 (7.0)	0.71 (0.55–0.90)
Yes	4/165 (2.4)	13/162 (8.0)	0.28 (0.09–0.87)
Type of oral anticoagulation at baseline			
Direct oral anticoagulation	27/674 (4.0)	51/705 (7.2)	0.54 (0.34–0.86)
Vitamin K antagonist	28/541 (5.2)	44/542 (8.1)	0.62 (0.39–1.00)
Neither	59/1164 (5.1)	73/1144 (6.4)	0.79 (0.56–1.12)
CHA_2DS_2-VASc score			
≤4	45/1417 (3.2)	77/1403 (5.5)	0.57 (0.40–0.82)
>4	69/962 (7.2)	91/988 (9.2)	0.77 (0.56–1.06)
Surgery type			
Any valve procedure	87/1565 (5.6)	134/1614 (8.3)	0.66 (0.50–0.86)
All other procedures	27/814 (3.3)	34/777 (4.4)	0.76 (0.46–1.26)
Ablation of atrial fibrillation			
No	80/1570 (5.1)	117/1638 (7.1)	0.71 (0.54–0.95)
Yes	34/809 (4.2)	51/753 (6.8)	0.60 (0.39–0.92)
History of hypertension			
No	16/419 (3.8)	33/450 (7.3)	0.51 (0.28–0.93)
Yes	98/1960 (5.0)	135/1941 (7.0)	0.71 (0.55–0.92)
History of heart failure			
No	38/1031 (3.7)	55/1019 (5.4)	0.67 (0.45–1.02)
Yes	76/1348 (5.6)	113/1372 (8.2)	0.68 (0.51–0.90)
Left ventricular ejection fraction			
≥50%	74/1508 (4.9)	107/1519 (7.0)	0.68 (0.51–0.92)
<50%	32/671 (4.8)	44/669 (6.6)	0.72 (0.46–1.13)
Previous stroke, TIA, or systemic embolism			
No	86/1988 (4.3)	126/1998 (6.3)	0.67 (0.51–0.89)
Yes	28/391 (7.2)	42/393 (10.7)	0.67 (0.42–1.09)
Atrial fibrillation or flutter			
No	40/904 (4.4)	55/958 (5.7)	0.76 (0.51–1.14)
Yes	74/1470 (4.4)	112/1429 (7.8)	0.63 (0.47–0.85)
Overall	114/2379 (4.8)	168/2391 (7.0)	0.67 (0.53–0.85)

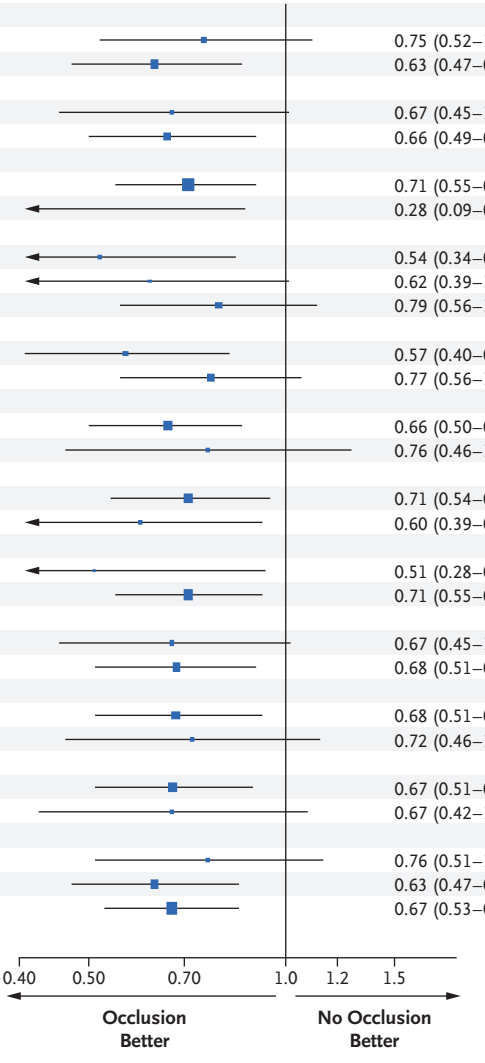

Figure 2. Subgroup Analysis of the Effect of Left Atrial Appendage Occlusion or No Occlusion on Stroke or Systemic Arterial Embolism.

The sizes of the squares are proportional to the precision of the estimates. The widths of the 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. Atrial fibrillation or flutter is based on the rhythm at baseline electrocardiography, and the comparator is any other rhythm. Scores on the CHA_2DS_2-VASc scale reflect the risk of stroke among patients with atrial fibrillation; scores range from 0 to 9, with higher scores indicating greater risk. TIA denotes transient ischemic attack.

DISCUSSION

In LAAOS III, among participants with atrial fibrillation and risk factors for stroke, the risk of the composite outcome of ischemic stroke or systemic thromboembolism was lower with concomitant left atrial appendage occlusion performed during cardiac surgery than without it. On the basis of the Kaplan–Meier estimates, the number of participants — with characteristics similar to those enrolled in the current trial — needed to undergo concomitant left atrial appendage occlusion during cardiac surgery to prevent one stroke over the period of 5 years was

37 (95% CI, 22 to 111). Several methods were used to perform concomitant occlusion during cardiac surgery, most of which incurred minimal additional cost and were performed without perioperative complications. No significant increase in the risk of heart failure or major bleeding was observed with the procedure.

The left atrial appendage is a source of atrial natriuretic peptide, and it has been hypothesized that removal of the appendage might impair renal clearance of salt and water, thereby increasing the risk of heart failure.[10,11] A recent nonrandomized study has supported this hypothesis.[12] In our trial, we did not observe an increase in hospitalization for heart failure, either early after surgery or during long-term follow-up.

Anticoagulation is the mainstay of stroke prevention in patients with atrial fibrillation[13] because it is highly effective. Vitamin K antagonists reduce the risk of stroke by two thirds, and direct oral anticoagulants are even more effective.[14] Although anticoagulation is limited by the increased risk of bleeding, guidelines conclude that the risk–benefit analysis strongly favors lifetime use of oral anticoagulation in the majority of higher-risk patients. Despite these well-established benefits, anticoagulation is limited by problems that include incorrect dosing, temporary interruptions for medical reasons, nonadherence to the prescribed therapy, and, for vitamin K antagonists, poor control of the international normalized ratio.[15] Surgical occlusion of the left atrial appendage reduces the risk of stroke by means of a different mechanism from that of anticoagulants, and its effects appear to be additive to those of oral anticoagulation. These additive effects are at least partly due to the continuous and permanent protection against embolic stroke provided by the procedure, which addresses some of the limitations of long-term anticoagulation.

We observed a high rate of stroke in the first 30 days after surgery as compared with the rest of follow-up. This finding is consistent with observations in other studies examining the risk of stroke among patients undergoing cardiac surgery.[16] Analyses of the primary outcome in our trial suggested a larger difference between the trial groups after 30 days than during the first 30 days (with hazard ratios of 0.82 [95% CI, 0.57 to 1.18] during the first 30 days after surgery and 0.58 [95% CI, 0.42 to 0.80] after 30 days). Early after surgery, some strokes are probably related to the surgery itself (e.g., aortic and intracardiac manipulation), factors against which occlusion is not likely to be effective. After the perioperative period, a greater proportion of strokes are caused by cardiac thromboembolism related to atrial fibrillation, for which occlusion is effective.

LAAOS III did not compare left atrial appendage occlusion with anticoagulation, and it would be incorrect to conclude that occlusion at the time of surgery should be considered as a replacement for anticoagulation. Whereas anticoagulation reduces the risk of stroke by approximately two thirds,[17] in LAAOS III, concomitant occlusion reduced the risk of stroke by approximately one third. A factor that offsets the possibly smaller reduction in the risk of ischemic stroke with left atrial appendage occlusion is the anticoagulant-related risk of hemorrhagic stroke, a risk that is not present in patients who undergo surgical occlusion and do not receive oral anticoagulants. Without a trial that directly compares oral anticoagulation with left atrial appendage occlusion, it remains uncertain whether occlusion can replace anticoagulation. Our trial therefore does not support concomitant surgical occlusion as a replacement for oral anticoagulation.

The results of LAAOS III have important implications for the use of nonpharmacologic therapies to prevent embolic stroke. In our trial, surgical occlusion of the left atrial appendage provided additional protection against stroke when added to anticoagulation. Percutaneous endovascular occlusion devices may also be effective as a complement to anticoagulation rather than as a replacement, but this would require testing. There are notable differences between surgical occlusion of the left atrial appendage and occlusion performed with a percutaneous endovascular device. Surgical occlusion is an extravascular procedure, whereas occlusion with an endovascular device may increase the risk of thrombus formation and embolism.

Limitations of our trial include the lack of information about the relative efficacy of left atrial appendage occlusion as compared with oral anticoagulation. Furthermore, the findings from LAAOS III apply primarily to surgical occlusion of the appendage performed as a con-

comitant procedure and not to stand-alone surgical or endovascular occlusion. We cannot discern from our results whether all surgical closure methods are comparable, and we did not examine whether occlusion was sustained over follow-up.

This trial showed that among patients with atrial fibrillation who had undergone cardiac surgery, most of whom continued to receive ongoing antithrombotic therapy, the risk of stroke or systemic embolism was lower with concomitant left atrial appendage occlusion performed during the surgery than without it.

Supported by the Canadian Institutes of Health Research, the Canadian Stroke Prevention Intervention Network, Hamilton Health Sciences Research Institute through the Population Health Research Institute, the Heart and Stroke Foundation of Canada, the Request for Applications Program–Research Strategic Initiatives of Hamilton Health Sciences, the Canadian Network and Centre for Trials Internationally, and McMaster University Surgical Associates.

Dr. Whitlock reports receiving grant support from Bayer and Roche, grant support and honoraria from Boehringer Ingelheim, and consulting fees from AtriCure and PhaseBio; Dr. Belley-Cote, receiving grant support from Bayer and Roche; Dr. Healey, receiving grant support and lecture fees from Boston Scientific; Dr. Sharma, receiving grant support and consulting fees from Bayer, grant support and fees for trial leadership from Bristol-Myers Squibb, and fees for trial leadership from Portola; Dr. Budera, receiving consulting fees from AtriCure; Dr. Devereaux, receiving grant support form Abbott Diagnostics, Boehringer Ingelheim, Roche Diagnostics, and Siemens and donated products from Philips Healthcare; Dr. Boening, receiving grant support and advisory board fees from Somahlution, advisory board fees from Nordic Pharma, grant support and honoraria from Zoll, honoraria from Abiomed, and consulting fees from B. Braun; Dr. Alings, receiving grant support from Sanofi and Bristol-Myers Squibb, committee fees from Pfizer, and advisory board fees from Portola, Boehringer Ingelheim, and Milestone; Dr. Mazer, receiving advisory board fees from Amgen, AstraZeneca, Boehringer Ingelheim, and Octapharma; and Dr. Connolly, receiving grant support, consulting fees, and lecture fees from Boehringer Ingelheim and Bristol-Myers Squibb, grant support and consulting fees from Sanofi Aventis, consulting fees from Portola, and grant support from Boston Scientific. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Richard P. Whitlock, M.D., Ph.D., Emilie P. Belley-Cote, M.D., Ph.D., Domenico Paparella, M.D., Jeff S. Healey, M.D., Katheryn Brady, B.Sc., Mukul Sharma, M.D., Wilko Reents, M.D., Petr Budera, M.D., Ph.D., Andony J. Baddour, M.D., Ph.D., Petr Fila, M.D., Ph.D., P.J. Devereaux, M.D., Ph.D., Alexander Bogachev-Prokophiev, M.D., Ph.D., Andreas Boening, M.D., Kevin H.T. Teoh, M.D., Georgios I. Tagarakis, M.D., Ph.D., Mark S. Slaughter, M.D., Alistair G. Royse, M.D., Shay McGuinness, M.B., Ch.B., Marco Alings, M.D., Ph.D., Prakash P. Punjabi, F.R.C.S., C. David Mazer, M.D., Richard J. Folkeringa, M.D., Ph.D., Andrea Colli, M.D., Álvaro Avezum, M.D., Ph.D., Juliet Nakamya, Ph.D., Kumar Balasubramanian, M.Sc., Jessica Vincent, M.Sc., Pierre Voisine, M.D., Andre Lamy, M.D., Salim Yusuf, F.R.S.C., D.Phil., and Stuart J. Connolly, M.D.

The authors' affiliations are as follows: McMaster University (R.P.W., E.P.B.-C., J.S.H., M.S., P.J.D., J.N., K. Balasubramanian, A.L., S.Y., S.J.C.), Hamilton Health Sciences (R.P.W., E.P.B.-C., J.S.H., K. Brady, M.S., P.J.D., J.V., A.L., S.Y., S.J.C.), and the Population Health Research Institute (R.P.W., E.P.B.-C., J.S.H., K. Brady, M.S., P.J.D., J.N., K. Balasubramanian, J.V., A.L., S.Y., S.J.C.), Hamilton, ON, Southlake Regional Health Centre, Newmarket, ON (K.H.T.T.), the University of Toronto and Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto (C.D.M.), and Quebec Heart and Lung Institute, Quebec, QC (P.V.) — all in Canada; University of Foggia, Foggia (D.P.), Santa Maria Hospital, Gruppo Villa Maria Care and Research, Bari (D.P.), and the University of Pisa, Pisa (A.C.) — all in Italy; Rhön-Klinikum Campus Bad Neustadt, Bad Neustadt (W.R.), and University Hospital Giessen, Giessen (A.B.) — both in Germany; the Institute for Clinical and Experimental Medicine, Prague (P.B.), and the Center of Cardiovascular Surgery and Transplantation, Brno (P.F.) — both in the Czech Republic; "G. Papanikolaou" Hospital (A.J.B.) and Aristotle University of Thessaloniki (G.I.T.) — both in Thessaloniki, Greece; E. Meshalkin National Medical Research Center, Novosibirsk, Russia (A.B.-P.); the University of Louisville, Louisville, KY (M.S.S.); the University of Melbourne and Royal Melbourne Hospital, Melbourne, VIC, Australia (A.G.R.); Auckland City Hospital, Auckland, New Zealand (S.M.); Amphia Ziekenhuis, Breda (M.A.), and Medical Center Leeuwarden, Leeuwarden (R.J.F.) — both in the Netherlands; the National Heart and Lung Institute, Imperial College London, London (P.P.P.); and the International Research Center, Hospital Alemão Oswaldo Cruz, São Paulo (Á.A.).

REFERENCES

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370-5.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-8.
3. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004;110:2287-92.
4. Stroke Prevention in Atrial Fibrillation Study: final results. Circulation 1991;84:527-39.
5. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755-9.
6. Whitlock R, Healey J, Vincent J, et al. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. Ann Cardiothorac Surg 2014;3:45-54.
7. Jones WJ, Williams LS, Meschia JF. Validating the Questionnaire for Verifying Stroke-Free Status (QVSFS) by neurological history and examination. Stroke 2001;32:2232-6.
8. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the Ameri-

can Heart Association/American Stroke Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, and the Interdisciplinary Council on Peripheral Vascular Disease: the American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40:2276-93.

9. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.

10. Wilber DJ. Neurohormonal regulation and the left atrial appendage: still more to learn. J Am Coll Cardiol 2018;71:145-7.

11. Lakkireddy D, Turagam M, Afzal MR, et al. Left atrial appendage closure and systemic homeostasis: the LAA HOMEOSTASIS study. J Am Coll Cardiol 2018;71:135-44.

12. Mahmood E, Matyal R, Mahmood F, et al. Impact of left atrial appendage exclusion on short-term outcomes in isolated coronary artery bypass graft surgery. Circulation 2020;142:20-8.

13. Fuster V, Rydén LE, Cannom DS, et al. Guidelines for the management of patients with atrial fibrillation: executive summary. Rev Esp Cardiol 2006;59:1329. (In Spanish.)

14. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.

15. Perreault S, de Denus S, White-Guay B, et al. Oral anticoagulant prescription trends, profile use, and determinants of adherence in patients with atrial fibrillation. Pharmacotherapy 2020;40:40-54.

16. Salazar JD, Wityk RJ, Grega MA, et al. Stroke after cardiac surgery: short- and long-term outcomes. Ann Thorac Surg 2001;72:1195-202.

17. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.