Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTARY APPENDIX

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2 Definitions of Outcome Events

Stroke
Diagnosis of stroke requires new focal neurological symptoms with rapid onset, lasting at least 24 hours. All strokes are classified as definite ischemic, definite hemorrhagic or type uncertain. Transient ischemic attacks (TIAs) with positive neuroimaging are upgraded to stroke during blinded outcome adjudication. TIA with positive neuroimaging is classified as a stroke, regardless of duration of symptoms and per the 2014 ACC/AHA definition. The definiton of positive neuroimaging is any imaging evidence of acute cerebral ischemia compatible with the symptoms and physical findings.

Transient Ischemic Attack (TIA)
An episode of a new focal neurologic deficit with rapid onset with signs or symptoms lasting <24 hours.

Systemic Arterial Embolism
Systemic arterial embolism is judged to occur where there is a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries), which is supported by objective evidence of embolism.

Major bleed
Major bleeding **within the first 48 hours after surgery** is defined as per BARC Type 4: 1) Perioperative intracranial bleeding within 48 hours; and/or 2) Reoperation after closure of sternotomy for the purpose of controlling bleeding; and/or 3) Transfusion of ≥ 5 units whole blood or packed red blood cells within a 48 hour period (note: cell saver products are not counted); and/or 4) Chest tube output ≥ 2L within a 24 hour period.

Major bleeding **after 48 hours after surgery** is defined as per modified ISTH: 1) Fatal bleeding, and/or 2) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or 3) Bleeding causing a fall in hemoglobin level of 3.0 g/dL* or more, or leading to transfusion of two or more units of whole blood or red cells.
* corrected for transfusion (1 unit PRBC or 1 unit whole blood = 1 g/dL hemoglobin)

Hospitalization with Heart Failure
Re-hospitalization with an overnight stay or prolongation of an existing hospitalization due to heart failure which requires both clinical (i.e. any of the following signs: elevated jugular venous pressure, respiratory râles, crepitations, or presence of S3) and radiographic evidence (e.g. vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

Efficacy of Occlusion Technique
Successful occlusion is defined as TEE Doppler assessment demonstrating an absence of flow across the suture line and a stump of <1 cm.

Sub-Classification of Death

All deaths are classified as either cardiovascular or non-cardiovascular. Cardiovascular death is defined as any death with a cardiovascular cause and includes those deaths occurring within 30 days of a cardiovascular procedure (e.g. cardiac surgery, percutaneous transluminal coronary angioplasty), cardiac arrest, myocardial infarction, pulmonary embolus, stroke, hemorrhage, or deaths due to an unknown cause. Non-cardiovascular death is defined as deaths due to a clearly documented non-cardiovascular cause (e.g. trauma, infection, malignancy).

Myocardial Infarction

Perioperative MI (≤48 hours post-operatively) is defined as the presence of new Q-waves or a new left bundle branch block on electrocardiogram, combined with a biomarker (CK-MB or troponin) elevation of at least 5 times the upper reference limit. **Late MI** (>48 hours) is defined as ischemic symptoms, ECG changes consistent with myocardial infarction (new significant Q waves in two contiguous leads) or evolving ST-segment or T-wave changes in two contiguous leads signifying ischemia or new left bundle branch block (LBBB) or ST segment elevation and elevated cardiac markers (troponins or CK-MB) in the necrosis range. Myocardial injury occurring after a percutaneous coronary intervention (PCI) are included in the late perioperative MI group but are defined as elevation of cardiac markers at least 3 times upper limit of normal (ULN) within 24 hours of percutaneous coronary intervention (PCI) or characteristic evolution of new ECG changes.

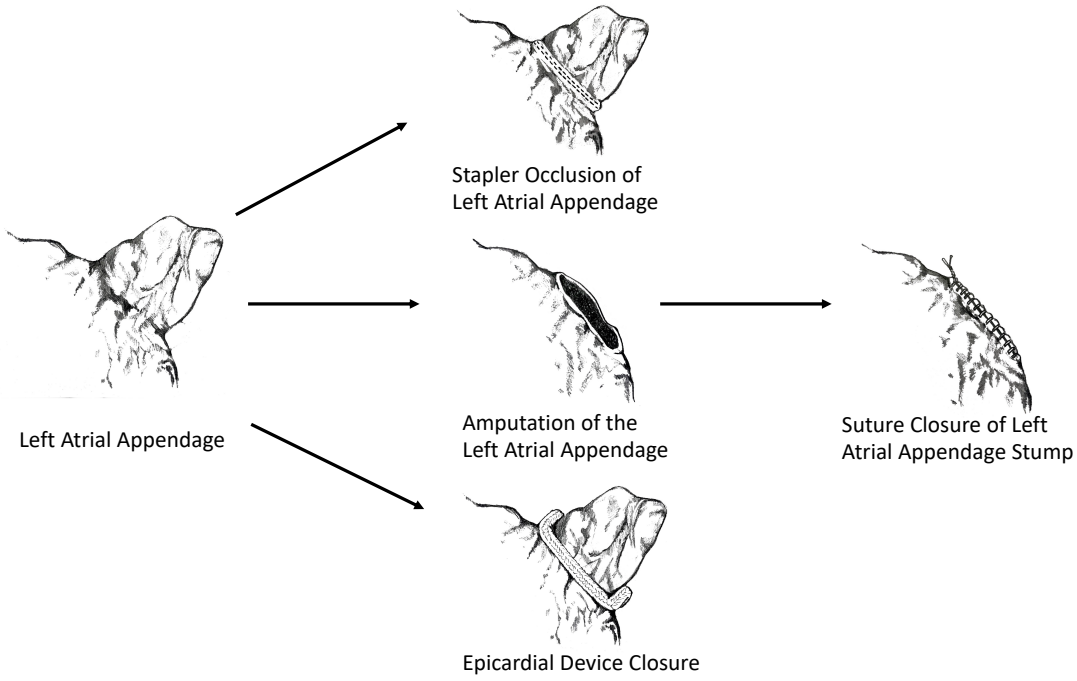
Transfusion Requirements

Autologous blood, homologous processed red blood cells, whole blood, plasma, platelets, cryoprecipitate are recorded for 24 hours after surgery.

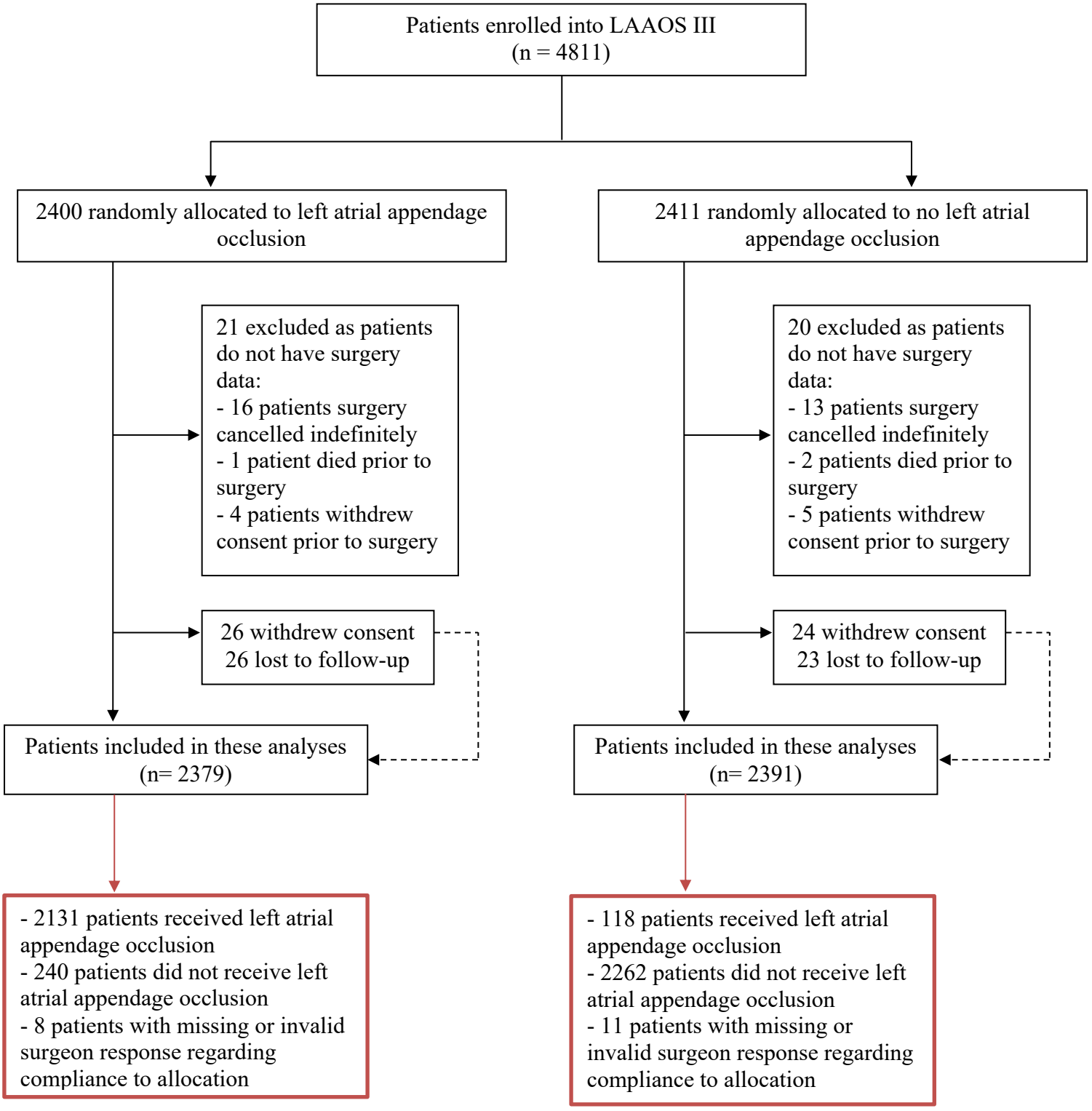
24-Hour Chest Tube Output

Total chest tube output in the first 24 hours or until the tubes are removed, whichever comes earlier.

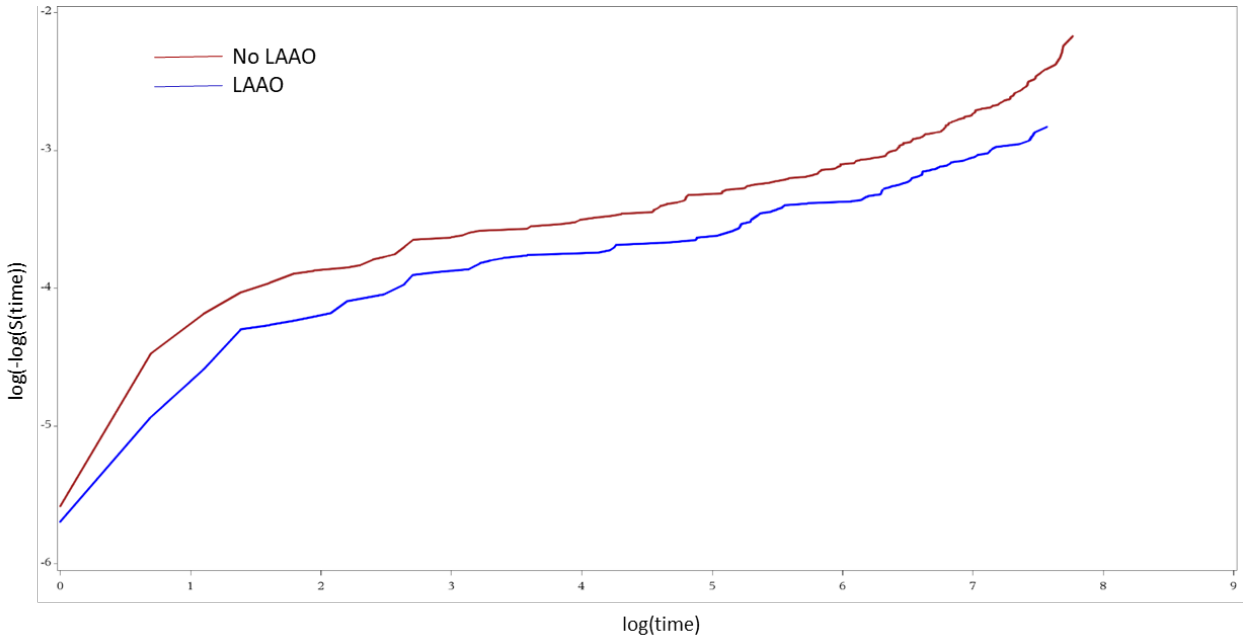
3 Figure S1: Epicardial occlusion techniques permitted within LAAOS III



4 Figure S2: Patient flow chart



5 Figure S3: Log-log plot for proportionality



A standard visual assessment of the proportionality assumption is done by applying a transformation of the Kaplan-Meier survival curve and plotting the function log(-log(survival)) as a function of log(time) for the treatment (LAAO vs No LAAO), where log represents the natural logarithm function [ref. Dabrowska et al 1992 Statistics in Medicine]. Proportional hazards would exhibit constant differences and approximate linear functions. We note that differences are constant and the functions are approximately linear except between 0 and 1 in the log(time) scale. Since time was measured in days, 1 in log(time) is equivalent to 2.7 days, so that the hazards were different in the first few days from the rest of the follow-up time, which is to be expected from a clinical standpoint. Nevertheless, to formally test whether the proportional hazards assumption was met or not, we tested the significance of the interaction effect between treatment and time and the result was non-significant (p=0.1817), so that the proportionality assumption was not violated.

6 Table S1: Anticoagulation during follow-up.

	Left Atrial Appendage Occlusion			No Left Atrial Appendage Occlusion		
	Any anticoagulation	**Vitamin K antagonist**	**Direct oral anticoagulant**	**Any anticoagulation**	**Vitamin K antagonist**	**Direct oral anticoagulant**
Discharge	83.4%	64.8%	18.6%	81.0%	62.6%	18.4%
One Year	79.6%	44.6%	35.0%	78.9%	43.2%	35.6%
Two Years	77.1%	39.2%	37.9%	77.7%	39.7%	38.0%
Three Years	75.3%	38.3%	37.0%	78.2%	39.4%	38.8%

7 Table S2: Causes of death in LAAOS III

	Left atrial appendage occlusion (N=2379)	No left atrial appendage occlusion (N=2391)
Death	538 (22.6%)	537 (22.5%)
Cardiovascular	310 (13.0%)	331 (13.8%)
- Myocardial Infarction	12 (0.5%)	14 (0.6%)
- Asystole	17 (0.7%)	23 (1.0%)
- Ventricular Tachyarrhythmia/Fibrillation	6 (0.3%)	6 (0.3%)
- Electromechanical Dissociation	1 (0.0%)	3 (0.1%)
- Other Sudden or Arrhythmic Death	24 (1.0%)	26 (1.1%)
- Congestive Heart Failure	51 (2.1%)	42 (1.8%)
- Stroke	23 (1.0%)	38 (1.6%)
- Hemorrhage	12 (0.5%)	17 (0.7%)
- Peripheral Vascular Disease	2 (0.1%)	1 (0%)
- Multiple Organ Failure	43 (1.8%)	52 (2.2%)
- Cardiogenic Shock	18 (0.8%)	23 (1.0%)
- Myocardial Free Wall Rupture	2 (0.1%)	1 (0%)
- Cardiac Tamponade	1 (0.0%)	3 (0.1%)
- Pulmonary Embolism	5 (0.2%)	0 (0%)
- Aortic Dissection/Rupture	1 (0.0%)	3 (0.1%)
- Abdominal Aortic Aneurysm	3 (0.1%)	4 (0.2%)
- Arterial Embolism	2 (0.1%)	0 (0.0%)
- Other Cardiovascular	13 (0.5%)	13 (0.5%)
- Unknown - Presumed Cardiovascular	74 (3.1%)	62 (2.6%)
Non-Cardiovascular	228 (9.6%)	206 (8.6%)
- Renal Failure	18 (0.8%)	17 (0.7%)
- Liver Failure	6 (0.3%)	4 (0.2%)
- Septic Shock/Sepsis	75 (3.2%)	68 (2.8%)
- Respiratory Failure	51 (2.1%)	38 (1.6%)
- Cancer	51 (2.1%)	57 (2.4%)
- Other Non-Cardiovascular	27 (1.1%)	22 (0.9%)

8 Table S3: Additional analyses of primary outcome

Outcome	Left atrial appendage occlusion		No left atrial appendage occlusion		HR	95% CI[††]
	Number of participants with event	Percent	Number of participants with event	Percent		
Ischemic stroke[†] or systemic embolism (including participants not operated on*)	114/2400	4.8	168/2411	7.0	0.67	0.53-0.85
Ischemic stroke[†] or systemic embolism (analysed per protocol**)	101/2131	4.7	156/2262	6.9	0.68	0.53-0.87
Ischemic stroke[†] or systemic embolism (analysed as treated***)	113/2249	5.0	169/2502	6.8	0.73	0.58-0.93
Primary outcome with death as competing risk****	114/2379	4.8	168/2391	7.0	0.68	0.53-0.86

Abbreviations: HR = hazard ratio, CI = confidence interval. [†] Ischemic stroke includes transient ischemic attack with positive neuroimaging. *The intention to treat including all participants analysis includes all participants, including those who did not undergo surgery (left atrial appendage occlusion n=2400, no left atrial appendage occlusion n=2411). **The per protocol analysis included only participants who received the treatment to which they were assigned at randomization (left atrial appendage occlusion n=2131, no left atrial appendage occlusion n=2262). ***The as treated analysis analyzed participants according to the treatment actually received (left atrial appendage occlusion n=2249, no left atrial appendage occlusion n=2502). ****Calculated hazard ratio is Subdistribution hazards calculated using Fine and gray method. [††]The widths of the intervals have not been adjusted for multiplicity and that any inferences drawn from these intervals may not be reproducible