The impact of surgical left atrial appendage amputation/ligation on stroke prevention in patients undergoing off-pump coronary artery bypass grafting

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This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
The authors had full control over the study design, methods used, outcome parameters and results, analysis of data, and production of the written report. This study was funded without assistance from industry sources. None of the authors received additional funds or aid related to or as a consequence of this study.

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Abstract

Stroke is a major adverse event in patients developing atrial fibrillation (AF) after cardiac surgery. Surgical left atrial appendage amputation/ligation (LAA-A/L) during off-pump coronary artery bypass grafting (OPCAB) is routinely performed in our institution.

We analyzed 578 consecutive patients (mean age 69 years, male 82%) undergoing OPCAB with or without concomitant LAA-A/L from 2011 to 2014 at our institution in a prospective observational manner. The safety and efficacy of the concomitant LAA-A/L on preventing early (<30 days) and overall postoperative stroke were examined.

A total of 193 patients (33.4%) underwent LAA-A/L, consisting of amputation in 154 and ligation in 39 patients (80% and 20% of the cases, respectively). Preoperative characteristics, operative time, requirement of blood transfusion, and 30-day mortality were not significantly different between those with and without LAA-A/L. The incidences of postoperative AF and early and overall stroke were not significantly different between the groups in the analysis based on a total cohort. In subanalysis of patients without LAA-A/L, early and overall stroke occurred more frequently in those developing postoperative AF than those without AF (2.8% vs. 0%; p=0.005, 6.2% vs. 1.5%; p=0.017, respectively), while in patients receiving LAA-A/L, stroke incidences did not differ between those with and without AF. Multivariate logistic regression showed postoperative AF without LAA-A/L as the only independent positive predictor of overall stroke (OR 3.69, p=0.03).

Concomitant LAA-A/L with OPCAB can safely prevent postoperative stroke occurrence in case patients develop AF, the most common arrhythmia associated with stroke.

Keywords: left atrial appendage, atrial fibrillation, stroke prevention, off-pump coronary artery bypass grafting

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, and its incidence increases with aging [1]. Approximately one-quarter of individuals are projected to develop AF in their lifetime [2]. AF increases the risk of stroke five-fold, independent of others factors, and it is attributed to 15% to 20% of all strokes [3]. Patients with paroxysmal AF have a similar risk for stroke and non-cerebral embolism compared with patients with sustained AF [4]. Indeed, AF is the most commonly encountered arrhythmia after cardiac surgery even in patients undergoing nonvalvular surgery [5-7]. Previous studies have indicated that 10% to 65% of patients undergoing cardiac surgery suffered from postoperative AF [6,8]. Bassano C et al. recently reported that neurological complications occur in patients developing postoperative paroxysmal AF, even in patients undergoing cardiac surgery without cardiopulmonary bypass [9].

There has been great discussion about whether the left atrial appendage (LAA) closure for patients with AF can reduce ischemic stroke [10-13]. In patients with AF, the most common place of thrombus is LAA. In valvular AF, 57% of left atrial thrombus occurred in LAA, whereas in nonvalvular AF, 90% of thrombi were located inside LAA [14]. It can be emphasized that the LAA closure is more effective for stroke prevention in nonvalvular AF. Recently, several transcatheter LAA closure devices have been developed to reduce the risk of stroke and obviate the need for long-term systemic anticoagulation therapy in patients with nonvalvular AF [15-17]. Implantation of the device was successful in more than 90% of cases [18-20]. However, procedure-related adverse events remain a problem to be solved; these include procedural complications (4.2%–8.7%), pericardial effusion requiring surgery (0.2%–1.6%), pericardial effusion with pericardiocentesis (1.5%–2.4%), procedure-related stroke (0.0%–1.1%), and device embolization (0.2%–0.7%) [18-20]. Surgical LAA closure as a concomitant procedure is expected to be a safe and logical approach to prevent possible AF-related stroke that may occur after cardiac surgery; it is a small additional procedure that does not significantly prolong the operative time [21]. However, whether surgical LAA closure can reduce the incidence of postoperative stroke still remains controversial [22]. Furthermore, the safety and benefit of adding a surgical LAA procedure without using cardiopulmonary bypass has not yet been investigated. In our institution, we have recently performed LAA-amputation/ligation (A/L) in a routine manner in patients undergoing off-pump coronary artery bypass grafting (OPCAB). Therefore, in the present study, we investigated the efficacy for stroke prevention and the safety of concomitant LAA-A/L in patients receiving OPCAB at our institution.

Materials and methods

This is a single-center prospective observational study, analyzing a total of 606 consecutive patients undergoing coronary artery bypass grafting (CABG) at Juntendo University Hospital (Tokyo, Japan) between 2011 and 2014. Patients who had on-pump beating/arrest CABG or required conversion to on-pump from OPCAB were excluded from the analysis; scheduled on-pump beating/arrest CABG were in 24 patients, and unexpected conversion from OPCAB occurred in 4 patients (Fig. 1). The remaining patients undergoing OPCAB were investigated. Data collection methods for this study were approved by the Institutional Review Board at Juntendo University, and written informed consents were obtained from all patients.

At our institution, concomitant LAA-A/L with OPCAB has been routinely performed mainly since March 2013. The procedure was done manually in all patients of this study, and no device was used to close the LAA. The LAA is occluded in two manners: (i) amputation or (ii) ligation (Fig. 2) [23]. (i) The LAA is resected after tying up a 4-0 polypropylene purse-string suture encircling LAA. The stump is reinforced by a running suture going from the knot side to the other side and back again. (ii) The LAA is ligated after tying up a 4-0 polypropylene purse-string suture encircling LAA. Intraoperative transesophageal echocardiogram is performed to confirm complete closure of the LAA without any residual flow to the remaining structure. When we initially started this procedure, we applied it to patients requiring cardiopulmonary bypass for the surgery. The indication was later expanded to patients undergoing OPCAB. In principle, LAA-amputation is performed; however, in cases of unstable preoperative condition, LAA-ligation is adapted. The final decision of whether or not to perform this procedure and which manner to be adapted was made in the operation room based on the surgeon's preference. This may be the limitation of a prospective observational study. Since this was an observational study, we neither included nor excluded patients with any particular status. In addition, due to the nature of the non-randomized study, we were unable to apply a particular technique and/or medications to all patients.

We compared preoperative patients' characteristics; peri- and postoperative courses including stroke and AF incidences were compared between those with and without concomitant LAA-A/L. In addition, factors associated with postoperative stroke were investigated.

In the present study, the impact of LAA-A/L on early and overall stroke occurrences was investigated as a study endpoint. Furthermore, patients were stratified according to the presence or absence of postoperative AF, and its association with stroke in addition to LAA-A/L procedure was analyzed. Early postoperative stroke was defined as stroke occurring within 30 days postoperatively, including transient ischemic attack associated with focal or global neurological deficit that resolves within 24 hours. Preoperative and postoperative AF included paroxysmal or persistent AF, as well as pacemaker requirements for AF with bradycardia. Hypertension was defined as systolic blood pressure of ≥150 mm Hg, diastolic BP of ≥90 mm Hg, or both on more than two separate occasions, or status under antihypertensive medications. Dyslipidemia was defined as elevated low-density lipoprotein cholesterol levels (≥140 mg/dL) or a medically treated condition. Peripheral arterial disease was defined as claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries, or carotids. Diabetes was defined as HbA1c≧6.5% 〔NGSP〕 or a status under antidiabetic agents/insulin requirement. Renal dysfunction was defined as estimated glomerular filtration rate <60ml/min/1.73m^2. Preoperative CHADS2 and CHA2DS2-VASc scores were calculated [24], as these scores can predict ischemic stroke even in patients without a history of arrhythmia [25]. As a surgical risk assessment, EuroSCORE II was calculated in all patients [26].

Perioperative information including operative time, requirement of blood transfusion, duration of stay in the intensive care unit (ICU), and postoperative hospital stay; 30-day mortality, and re-exploration for bleeding were also compared between patients with and without LAA-A/L procedure in order to evaluate the safety of this procedure.

Overall stroke was considered as the combination of stroke during the early postoperative period and those occurring more than 30 days after the surgery, information about which was collected at a clinic visit or through a telephone interview; however, 35 patients (6.1%) were lost to follow-up. Mean follow-up was 2.1 ± 1.1 years (median: 2.11; max-min: 0.02-4.14).

We attempt to restore sinus rhythm in the majority of patients who develop postoperative AF by the use of beta-blockers as a first choice, and patients were treated with anticoagulation (heparin) within 24 hours of the onset of AF. Additional treatments to convert AF to sinus rhythm are antiarrhythmic drugs, including calcium channel blockers and amiodarone, and electrical cardioversion. Warfarin or novel oral anticoagulants (OACs) are administered at discharge in patients with sustained AF or frequent episodes of paroxysmal AF.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) for a normal distribution, but median (25 percentile–75 percentile) for a non-normal distribution. Categorical variables are presented as proportions. Normality was evaluated for each variable from normal distribution plots and histograms. Variables were compared between the groups with Student's unpaired two-tailed t-test. The Mann-Whitney test was performed with median and interquartile values when the variables were not normally distributed. Categorical variables were compared using the chi-square test. The predictors of early and overall postoperative stroke were analyzed using logistic regression analysis. The variables with p value <0.20 in univariate analysis were entered into the final multivariate model. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All tests were two-tailed. A p value <0.05 was considered to be statistically significant. Statistical analyses were performed using the Statistical Analysis System Software JMP

11.0 (SAS Institute Inc. Cary, NC, USA).

Results

Among a total of 606 patients who underwent CABG during the study period, 578 patients received OPCAB. Concomitant LAA-A/L with OPCAB was performed in 193 patients (33.4%) consisting of amputation in 154 and ligation in 39 patients (80% and 20% of the cases, respectively). The remaining 385 patients (66.6%) did not receive the LAA-A/L procedure (Isolated OPCAB group) (Fig. 1).

Table 1 compares the preoperative baseline clinical characteristics and operative information. There were more patients with hypertension in the isolated OPCAB group than in the concomitant LAA-A/L group. The proportion of patients with dyslipidemia was significantly higher in the concomitant LAA-A/L group. The proportions of patients with previous stroke and peripheral arterial disease were not significantly different between the groups. No differences were seen in the mean $CHADS_2$ score, CHA_2DS_2-VASc, or EuroSCORE II value between the groups.

Table 2 shows the incidences of postoperative AF and stroke occurrences. Approximately 30% of patients developed AF after OPCAB, and the incidence was not significantly different between patients who did or did not undergo the LAA-A/L procedure. Regarding medications, there was no significant difference in the proportion of patients receiving anticoagulants including warfarin and novel OACs, as well as aspirin or beta-blockers.

When we analyzed the postoperative early and overall stroke incidences without considering their rhythm status, neither incidence differed significantly between the groups. In contrast, by stratifying patients according to the presence or absence of postoperative AF, neither early nor overall stroke incidences were significantly different between those with and without AF in the concomitant LAA-A/L group, whereas the event rates were significantly higher in patients developing AF than those not developing AF in the isolated OPCAB group. A stroke occurred in 6 patients in the isolated OPCAB group developing postoperative AF; among those, 4 cases had a stroke several months postoperatively (mean 598 days postoperatively).

Table 3 shows the results of uni- and multivariate logistic regression analysis to find the factors associated with overall postoperative stroke, including preoperative demographics, with or without LAA-A/L procedure and postoperative AF. Univariate analysis revealed that the presence of peripheral artery disease and postoperative AF had a tendency of association with postoperative stroke ($p<0.20$), and the combination of postoperative AF without LAA-A/L procedure was the only factor statistically associated with stroke; therefore, these variables were entered into the multivariate analysis. Multivariate analysis was performed in two different models, one using postoperative AF alone as a covariable and the other using a combination of postoperative AF and LAA-A/L as a covariable. In multivariate logistic regression analysis, postoperative AF without LAA-A/L was the only and independent positive predictor of overall stroke (OR: 3.69; 95% CI: 1.18 to 10.92; $p=0.03$).

In order to evaluate the safety of the LAA-A/L procedure, we compared mortality and morbidity other than stroke and AF between patients who did and did not undergo the procedure (Table 4). In the concomitant LAA-A/L group, a mean of 3.4 distal anastomoses per patient was performed, and in the isolated OPCAB group, a mean of 3.2 distal anastomoses was performed ($p=0.03$). However, the length of operative time was similar in the two groups.

There were no differences in patients' distribution requiring intraoperative and postoperative blood transfusion between the groups. Re-exploration for bleeding was not observed in both groups. No significant differences in the length of ICU and postoperative hospital stay were noted between groups. The 30-day mortality was low and did not differ significantly between the groups.

Discussion

In the present investigation, we have, for the first time, demonstrated that concomitant LAA-A/L at the time of OPCAB reduces the incidence of stroke in patients developing postoperative AF without incremental risk.

Cardioembolic stroke is a major cause of morbidity and mortality in patients with AF, and

AF incidence increases with age [1,27,28]. In addition, because of the aging of the population and recent advances in cardiac surgery, an increasing number of elderly individuals who are at risk of developing AF postoperatively are now undergoing cardiac surgery including coronary artery bypass surgery [29]. Indeed, postoperative stroke is the most devastating adverse event in the elderly population. Warfarin and novel OACs have been proven to prevent stroke [30-33]. However, multiple problems with warfarin have been identified, including bleeding, multiple medication and food interaction, patient medical adherence, and the need for routine monitoring [32,34]. Although novel OACs do not require ongoing monitoring, they pose issues with cost and lack of an available antidote [33]. Consequently, administering warfarin or novel OACs to patients soon after cardiac surgery is not appropriate in some cases, and long-term use of such oral anticoagulant medications, especially in the elderly population, may come with a risk of bleeding as well as poor drug-adherence.

As the LAA is the prominent source of clot formation, techniques for elimination of the LAA has been widely discussed in various stages of development and early clinical use [35,36]. Recently, percutaneous LAA closure using devices has been shown as an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with nonvalvular AF [15-17]. However, there have been several reports showing that residual peri-device flow into the LAA after closure device placement was common, and it may be associated with thromboembolism formation around the device [17,37-38]. From this perspective, surgical LAA closure is an ideal method to accomplish complete elimination of the flow to LAA; however, its safety, especially without using cardiopulmonary bypass machine, and its efficacy of preventing stroke have not yet been fully elucidated. In patients suffering from nonvalvular AF, autopsy and surgical data have suggested that 90% of their atrial thrombi originate from the LAA [14]. Therefore, as we show, concomitant surgical LAA closure in patients receiving OPCAB is a reasonable procedure, considering the fact that AF has been recognized as the most frequent arrhythmia following coronary artery bypass surgery [39]

In this observation, although preoperative AF was found in approximately 4% of patients in both groups, postoperative AF was seen in almost 30% regardless of LAA-A/L procedure or pulmonary vein isolation. Our finding also indicated that postoperative AF was the only factor associated with stroke occurrence in the univariate logistic analysis. This result was consistent with a previous report that showed that postoperative AF was associated with more strokes (OR 2.02, p=0.001) and an independent predictor of long-term mortality, including transient postoperative AF [40,41]. Indeed, the incidence of strokes in patients developing AF without an LAA procedure was relatively high in our cohort (6.2%). Unfortunately, we were unable to detect their cardiac rhythm status at the time of the stroke; however, we assume that postoperative AF soon after surgery can also be associated with a stroke's occurrence in a late postoperative phase. Furthermore, analysis that combined LAA-A/L with the presence or absence of postoperative AF showed that stroke during both early and chronic postoperative periods occur more frequently in patients developing AF when they did not receive concomitant LAA-A/L than those at sinus rhythm, whereas the incidence did not differ between patients with AF and at sinus rhythm when they did receive the procedure. These results indicated that the LAA-A/L procedure could offset the risk of AF-associated stroke occurrence. Multivariate analysis indeed showed that patients developing postoperative AF without receiving the procedure had a more than 3.6-fold higher risk of stroke than those at sinus rhythm and those with AF receiving LAA-A/L. Therefore, we believe that performing concomitant LAA-A/L with OPCAB in a routine manner may be a beneficial option for patients requiring coronary revascularization, considering the prevalence of postoperative AF, as long as the procedure can be safely performed. The five-year results of the SYNTAX trial showed that CABG is a standard of care for patients with complex lesions [42]. Although the rate of procedure-related stroke was not significantly different between the CABG group and the percutaneous coronary intervention (PCI) group [42], patients undergoing CABG can receive concomitant LAA-A/L, which may reduce their future risk of developing stroke in a chronic phase following revascularization; thus, we speculate that CABG with LAA-A/L would be superior to PCI with regard to stroke prevention.

Regarding the safety of the procedure, previous reports proved that surgical LAA closure at the time of CABG could be performed without major adverse events [21]. However, off-pump

LAA-A/L has not been previously reported, and we believe that our present observation is the first detailed report of this procedure. We showed that concomitant LAA-A/L (i) did not lengthen operative time, (ii) did not increase the requirement of intraoperative and postoperative blood transfusion, (iii) did not prolong the duration of intensive care unit and hospital stay, and (iv) did not increase mortality as compared to OPCAB without LAA-A/L. However, in one of our case series, there was a patient who needed conversion from off-pump to on-pump due to bleeding, but he was able to be discharged home with no deficit. Moreover, surgical LAA-A/L does not require cost for device usage.

We perform concomitant surgical LAA-A/L without using devices in two different manners: amputation and ligation. Intraoperative transesophageal echocardiogram confirmed no residual LAA flow in LAA-ligation and no remnants of LAA in LAA-amputation. Amputation is the most successful technique of LAA closure, whereas ligation or stapler can often yield incomplete LAA closure, which can be associated with increased thromboembolic risk [43]. With respect to long-term residual LAA flow, amputation may be superior to ligation. Therefore, at our institution, LAA-amputation was actively performed, accounting for 80% of patients receiving LAA-A/L.

Study limitations

The strengths of our study include the relatively large sample size. The limitations include a selection bias of the study cohort due to the nature of the observational study without randomization, which caused some heterogeneity in the patients' characteristics, although we believe that the bias did not affect the results of the present analysis. Patient selection was dependent on the surgeons' preference. Secondly, we did not compare the safety and effect of concomitant LAA-A/L with anticoagulation on stroke prevention. Thirdly, all patients received intraoperative transesophageal echocardiogram; however, no investigation of leaking to LAA in the chronic postoperative phase was conducted. In some patients, we performed enhanced CT following surgery to evaluate the graft patency, which may be able to detect such leaking. Fourthly, we failed to classify postoperative rhythm status into paroxysmal AF, persistent AF, longstanding persistent AF, or permanent AF. Since this is the preliminary analysis, we believe that further observation should be necessary to investigate the impact of this procedure on stroke prevention from a long-term perspective.

Conclusions

Concomitant LAA-A/L at the time of OPCAB reduces the incidence of postoperative stroke in patients developing AF without incremental time, cost, or risk. Considering that AF is the most common arrhythmia and is frequent in the aging population, LAA-A/L as a routine procedure in OPCAB is beneficial.

Conflict of interest

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript.

References

1. Steger C, Pratter A, Martinek-Bregel M, Avanzini M, Valentin A, Slany J, Stöllberger C (2004) Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry. Eur Heart J 25:1734-1740
2. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J; American Heart Association Statistics Committee and Stroke Statistics Subcommittee (2011) Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation 123:e18-e209
3. P A Wolf, R D Abbott, W B Kannel (1991) Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 22:983-988
4. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, Connolly SJ; ACTIVE W Investigators (2007) Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. J Am Coll Cardiol 50:2156-2161

5. Yadava M, Hughey AB, Crawford TC (2014) Postoperative atrial fibrillation: incidence, mechanisms, and clinical correlates. Cardiol Clin 32:627-636
6. Maisel WH, Rawn JD, Stevenson WG (2001) Atrial fibrillation after cardiac surgery. Ann Intern Med 135:1061-1073
7. Frost L, Mølgaard H, Christiansen EH, Hjortholm K, Paulsen PK, Thomsen PE (1992) Atrial fibrillation and flutter after coronary artery bypass surgery: epidemiology, risk factors and preventive trials. Int J Cardiol 36:253-261
8. Rostagno C, La Meir M, Gelsomino S, Ghilli L, Rossi A, Carone E, Braconi L, Rosso G, Puggelli F, Mattesini A, Stefàno PL, Padeletti L, Maessen J, Gensini GF (2010) Atrial fibrillation after cardiac surgery: incidence, risk factors, and economic burden. J Cardiothorac Vasc Anesth 24:952-958
9. Bassano C, Bovio E, Uva F, Iacobelli S, Iasevoli N, Farinaccio A, Ruvolo G (2016) Partially anaortic clampless off-pump coronary artery bypass prevents neurologic injury compared to on-pump coronary surgery: a propensity score-matched study on 286 patients. Heart Vessels. 31:1412-1417
10. Price MJ, Valderrábano M (2014) Left atrial appendage closure to prevent stroke in patients with atrial fibrillation. Circulation 130:202-212
11. Cox JL (2013) Mechanical closure of the left atrial appendage: is it time to be more aggressive? J Thorac Cardiovasc Surg 146:1018-1027

12. Infante de Oliveira E (2013) What is the future for left atrial appendage closure? Rev Port Cardiol 32:473-475
13. Johnson WD, Ganjoo AK, Stone CD, Srivyas RC, Howard M (2000) The left atrial appendage: our most lethal human attachment! Surgical implications. Eur J Cardiothorac Surg 17:718-722
14. Orhan Onalan, Eugene Crystal (2007) Left Atrial Appendage Exclusion for Stroke Prevention in Patients With Nonrheumatic Atrial Fibrillation. Stroke 38:624-630
15. Ostermayer SH, Reisman M, Kramer PH, Matthews RV, Gray WA, Block PC, Omran H, Bartorelli AL, Della Bella P, Di Mario C, Pappone C, Casale PN, Moses JW, Poppas A, Williams DO, Meier B, Skanes A, Teirstein PS, Lesh MD, Nakai T, Bayard Y, Billinger K, Trepels T, Krumsdorf U, Sievert H (2005) Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. J Am Coll Cardiol 46:9-14
16. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators (2009) Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 374:534-542
17. Tzikas A, Shakir S, Gafoor S, Omran H, Berti S, Santoro G, Kefer J, Landmesser U, Nielsen-Kudsk JE, Cruz-Gonzalez I, Sievert H, Tichelbäcker T, Kanagaratnam P, Nietlispach F, Aminian A, Kasch F, Freixa X, Danna P, Rezzaghi M, Vermeersch P, Stock F, Stolcova M, Costa

M, Ibrahim R, Schillinger W, Meier B, Park JW (2016) Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. EuroIntervention 11:1170-1179

18. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, Holmes D; PROTECT AF Investigators (2013) Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. Circulation 127:720-729
19. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S (2011) Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation 123:417-424
20. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY (2014) Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol 64:1-12
21. Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, Hohnloser SH, Cybulsky I, Abouzahr L, Sawchuck C, Carroll S, Morillo C, Kleine P, Chu V, Lonn E, Connolly SJ (2005) Left Atrial Appendage Occlusion Study (LAAOS): Results of a randomized controlled pilot study of left

atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. Am Heart J 150:288-293

22. Dawson AG, Asopa S, Dunning J (2010) Should patients undergoing cardiac surgery with atrial fibrillation have left atrial appendage exclusion? Interact Cardiovasc Thorac Surg 10:306-311
23. Kato TS, Iwamura T, Endo D, Yokoyama Y, Oishi A, Shimada A, Yamamoto T, Kuwaki K, Inaba H, Amano A (2015) Left Atrial Appendage Closure Reduces the Incidence of Post-operative Cerebrovascular Accidents in Patients Undergoing Cardiac Surgery. Circulation J 79:2591-2597
24. Chua SK, Shyu KG, Lu MJ, Lien LM, Lin CH, Chao HH, Lo HM (2013) Clinical utility of CHADS2 and CHA2DS2-VASc scoring systems for predicting postoperative atrial fibrillation after cardiac surgery. J Thorac Cardiovasc Surg 146:919-926
25. Kondo T, Yamada T, Morita T, Furukawa Y, Tamaki S, Iwasaki Y, Kawasaki M, Kikuchi A, Kawai T, Takahashi S, Ishimi M, Hakui H, Ozaki T, Sato Y, Seo M, Sakata Y, Fukunami M (2016) The CHADS2 score predicts ischemic stroke in chronic heart failure patients without atrial fibrillation: comparison to other stroke risk scores. Heart Vessels. doi: 10.1007/s00380-016-0861-7
26. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U (2012) EuroSCORE II. Eur J Cardiothorac Surg 41:734-744
27. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, Van Gilst WH, Van Gelder IC, Rienstra M (2015) Incidence of Atrial Fibrillation and Relationship With

Cardiovascular Events, Heart Failure, and Mortality: A Community-Based Study From the Netherlands. J Am Coll Cardiol 66:1000-1007

28. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ (2004) Lifetime Risk for Development of Atrial Fibrillation. The Framingham Heart Study. Circulation 110:1042-1046
29. Natarajan A, Samadian S, Clark S (2007) Coronary artery bypass surgery in elderly people. Postgrad Med J 83:154-158
30. Hart RG, Pearce LA, Aguilar MI (2007) Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. Ann Intern Med 146:857-867
31. Dogliotti A, Paolasso E, Giugliano RP (2013) Novel oral anticoagulants in atrial fibrillation: a meta-analysis of large, randomized, controlled trials vs warfarin. Clin Cardiol 36:61-67
32. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361:1139-1151
33. Granger CB, Armaganijan LV (2012) Newer oral anticoagulants should be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation and risk factors for stroke or thromboembolism. Circulation 125:159-164
34. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT (2000) Why do patients with atrial

fibrillation not receive warfarin? Arch Intern Med 160:41-46

35. Sunil Kapur, Moussa Mansour (2014) Left Atrial Appendage Closure Devices For Stroke Prevention. Arrhythmia & Electrophysiology Review 3:25-29

36. Pison L, Potpara TS, Chen J, Larsen TB, Bongiorni MG, Blomström-Lundqvist C; Scientific Initiative Committee, European Heart Rhythm Association (2015) Left atrial appendage closure-indications, techniques, and outcomes: results of the European Heart Rhythm Association Survey. Europace 17:642-646

37. Viles-Gonzalez JF, Kar S, Douglas P, Dukkipati S, Feldman T, Horton R, Holmes D, Reddy VY (2012) The clinical impact of incomplete left atrial appendage closure with the Watchman Device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) substudy. J Am Coll Cardiol 59:923-929

38. Freixa X, Tzikas A, Sobrino A, Chan J, Basmadjian AJ, Ibrahim R (2013) Left atrial appendage closure with the Amplatzer™ Cardiac Plug: impact of shape and device sizing on follow-up leaks. Int J Cardiol 168:1023-1027

39. Aytemir K, Aksoyek S, Ozer N, Aslamaci S, Oto A (1999) Atrial fibrillation after coronary artery bypass surgery: P wave signal averaged ECG, clinical and angiographic variables in risk assessment. Int J Cardiol 69:49-56

40. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, Lopez JA, Rasekh A, Wilson JM,

Massumi A (2004) Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol 43:742-748

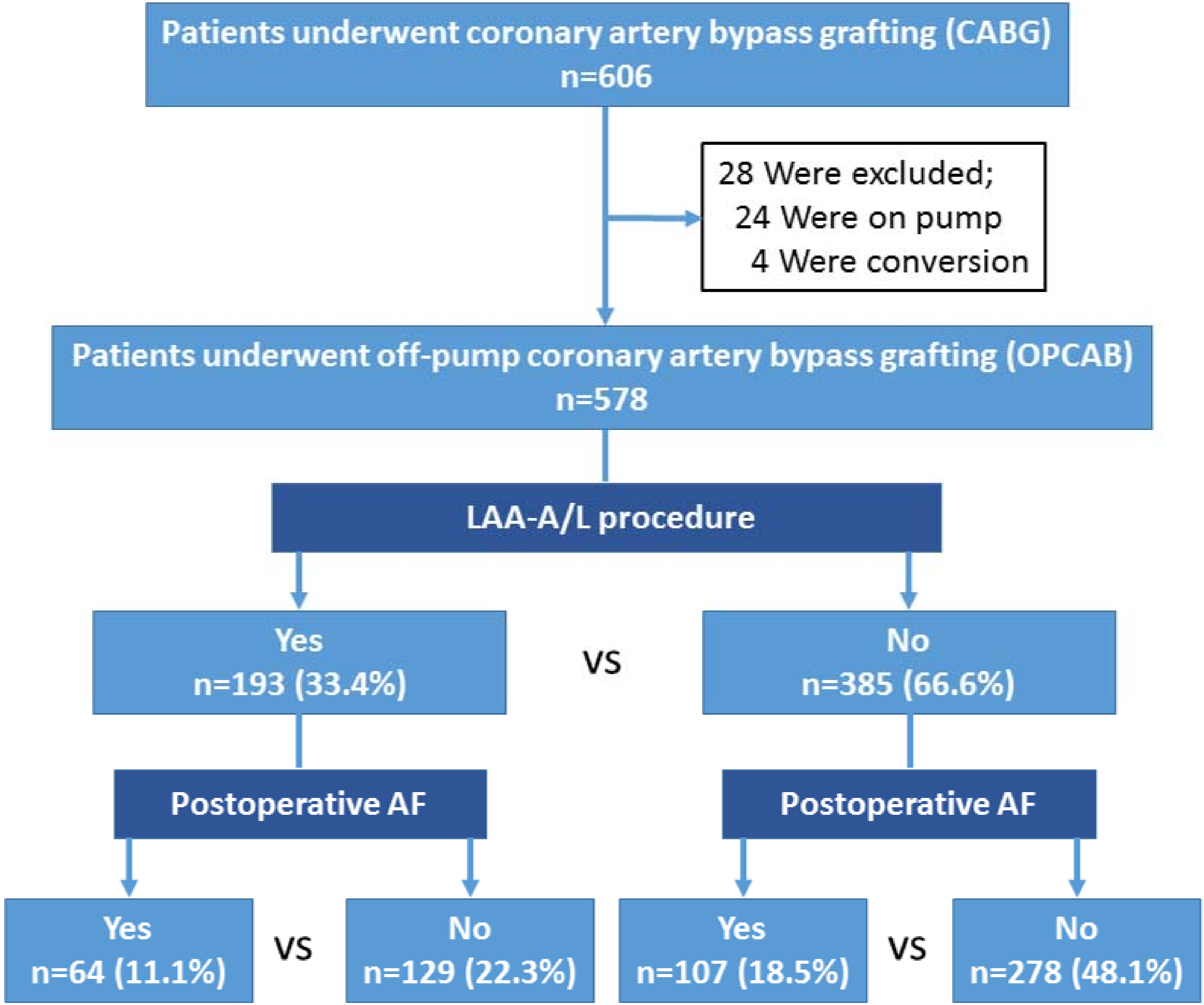
41. Philip F, Becker M, Galla J, Blackstone E, Kapadia SR (2014) Transient post-operative atrial fibrillation predicts short and long term adverse events following CABG. Cardiovasc Diagn Ther 4:365-372
42. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW (2013) Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 381:629–638
43. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL (2008) Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. J Am Coll Cardiol 52:924-929

Figure Legends

Fig. 1: Patient distribution.

Fig. 2: Surgical techniques of LAA-A/L.

First, the LAA is tied up to a 4-0 polypropylene purse-string suture encircling LAA. Second, the LAA is resected, which stump is reinforced by a running suture going from the knot side to the other side and back again (A) or is again ligated with 0 silk (B).


Patients underwent coronary artery bypass grafting (CABG)
n=606
28 Were excluded;
24 Were on pump
4 Were conversion
Patients underwent off-pump coronary artery bypass grafting (OPCAB)
n=578
LAA-A/L procedure
Yes
n=193 (33.4%)
VS
No
n=385 (66.6%)
Postoperative AF
Postoperative AF
Yes
n=64 (11.1%)
VS
No
n=129 (22.3%)
Yes
n=107 (18.5%)
VS
No
n=278 (48.1%)

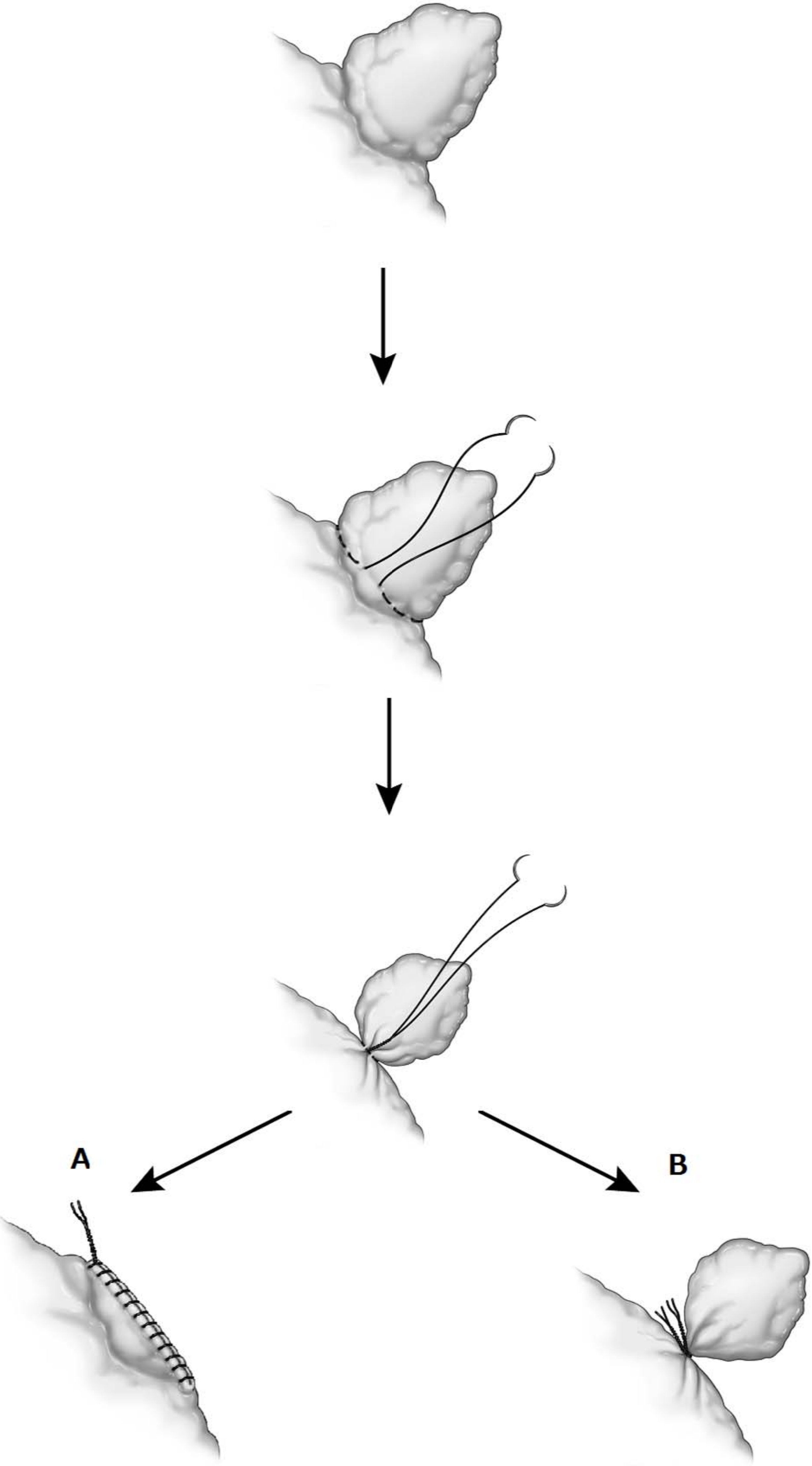

A
B

Table1: Baseline demographic characteristics and operative information.

	Concomitant LAA-A/L (n=193)	Isolated OPCAB (n=385)	p value
Characteristics			
Age, yrs	68.4 ± 10.0	68.6 ± 9.8	0.82
Male sex, n (%)	157 (81.4%)	314 (81.8%)	0.89
BMI, kg/m^2	24.1 ± 3.4	24.0 ± 3.4	0.85
Hypertension, n (%)	137 (71.0%)	305 (79.5%)	0.02
Hyperlipidemia, n (%)	149 (77.2%)	256 (66.5%)	0.008
Diabetes, n (%)	89 (46.1%)	206 (53.9%)	0.08
Requiring insulin, n (%)	38 (19.7%)	76 (20.0%)	0.93
Current smoker, n (%)	20 (10.4%)	57 (14.8%)	0.14
Peripheral arterial disease, n (%)	23 (11.9%)	51 (13.3%)	0.65
Renal dysfunction, n (%)	74 (38.3%)	150 (39.0%)	0.89
Hemodialysis, n (%)	16 (8.3%)	30 (7.8%)	0.83
Previous stroke, n (%)	26 (13.5%)	47 (12.2%)	0.67
Previous PCI, n (%)	50 (25.9%)	96 (24.9%)	0.80
DES, n (%)	37 (19.2%)	67 (17.4%)	0.40
Ejection fraction <30%, n (%)	8 (4.3%)	13 (3.6%)	0.65
Atrial fibrillation, n (%)	7 (3.6%)	14 (3.6%)	0.99
Left atrial diameter, mm	38.5 ± 5.3	38.0 ± 5.6	0.28
$CHADS_2$ score	1.9 ± 1.3	2.1 ± 1.2	0.18
CHA_2DS_2-VASc score	3.8 ± 1.5	4.0 ± 1.4	0.21
LMT or 3VD, n (%)	149 (77.2%)	276 (72.0%)	0.18
EuroSCOREII value	2.3 ± 2.2	2.5 ± 3.2	0.33
Surgical details			
Emergency or urgent, n (%)	23 (11.8%)	45 (11.7%)	0.94
No. of distal anastomosis	3.4 ± 1.2	3.2 ± 1.3	0.03

Pulmonary vein isolation, n (%)	2 (1.0%)	3 (0.8%)	0.75
IABP, n (%)	3 (1.6%)	4 (1.0%)	0.59

Abbreviations not described in text: BMI = body mass index; DES = drug eluting stent; IABP = intra-aortic balloon pump; LMT = left main trunk; 3VD = three-vessel disease.

Table 2: Incidences of postoperative AF, stroke, and medications.

	Concomitant LAA-A/L (n=193)			Isolated OPCAB (n=385)			p value
Postoperative AF, n (%)	64 (33.2%)			107 (27.8%)			0.18
Postoperative medications							
Anticoagulations, n (%)	13 (6.8%)			32 (8.4%)			0.50
Aspirin, n (%)	188 (97.9%)			375 (98.2%)			0.84
Thienopyridine, n (%)	17 (8.9%)			36 (9.4%)			0.82
beta-blockers, n (%)	141 (73.4%)			267 (70.0%)			0.39
ARBs, n (%)	11 (5.7%)			30 (7.8%)			0.36
Early stroke, n (%)	2 (1.0%)			3 (0.8%)			0.75
Overall stroke, n (%)	4 (2.2%)			10 (2.8%)			0.67
Early/Overall stroke Stratified by AF yes/no	Sinus	AF	p value	Sinus	AF	p value	
Early stroke, n (%)	1 (0.8%) (n=129)	1 (1.6%) (n=64)	0.61	0 (0%) (n=278)	3 (2.8%) (n=107)	0.005	
Overall stroke, n (%)	3 (2.5%) (n=121)	1 (1.6%) (n=63)	0.69	4 (1.5%) (n=263)	6 (6.2%) (n=97)	0.017	

Abbreviations not described in text: ARB = angiotensin II receptor blockers.

Table 3: Factors associated with overall postoperative stroke.

	Univariate		**Multivariate (Model 1)**		**Multivariate (Model 2)**	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age (years)	1.00 (0.95-1.06)	0.97				
Male sex (Male=1)	1.36 (0.36-8.86)	0.68				
BMI (kg/m^2)	0.98 (0.83-1.14)	0.80				
Hypertension (yes=1)	1.17 (0.36-5.23)	0.81				
Hyperlipidemia (yes=1)	0.74 (0.25-2.44)	0.61				
Diabetes (yes=1)	0.97 (0.33-2.89)	0.96				
Requiring insulin (yes=1)	1.64 (0.45-5.05)	0.43				
Current smoker (yes=1)	1.09 (0.17-4.12)	0.91				
Peripheral arterial disease (yes=1)	2.81 (0.75-8.66)	0.11	2.80 (0.75-8.64)	0.12	2.90 (0.77-9.07)	0.11
Renal dysfunction (yes=1)	1.61 (0.54-4.76)	0.38				
Hemodialysis (yes=1)	0.85 (0.05-4.41)	0.87				
Previous stroke (yes=1)	1.24 (0.19-4.66)	0.79				
Ejection fraction (%)	1.00 (0.96-1.04)	0.94				
Left atrial diameter (mm)	1.01 (0.92-1.11)	0.79				
LAA-A/L (yes=1)	0.78 (0.21-2.35)	0.67				
Postoperative AF (yes=1)	2.46 (0.83-7.29)	0.10	0.78 (0.21-2.38)	0.68		
Postoperative AF with LAA-A/L (yes=1)	0.58 (0.03-2.99)	0.58				
Postoperative AF without LAA-A/L (yes=1)	3.62 (1.16-10.63)	0.03			3.69 (1.18-10.92)	0.03

Model 1 used postoperative AF as a solitary covariable. Model 2 used a combination of postoperative AF and LAA-AL as a covariable.

Table 4: Postoperative mortality and morbidity other than stroke and AF.

	Concomitant LAA-A/L (n=193)	**Isolated OPCAB (n=385)**	**p value**
Operative time, min	259 ± 61	267 ± 71	0.14
ICU stay, day	1 (1-2)	1 (1-2)	0.38
Postoperative hospital stay, day	6 (5-8)	6 (5-8)	0.44
Requirement of intraoperative blood transfusion, n (%)	48 (24.9%)	108 (28.1%)	0.41
Requirement of postoperative blood transfusion, n (%)	34 (17.6%)	78 (20.4%)	0.43
Re-expolaration, n (%)	0	0	-
30-day mortality, n (%)	1 (0.5%)	1 (0.3%)	0.62
Overall mortality, n (%)	8 (4.3%)	29 (8.1%)	0.09