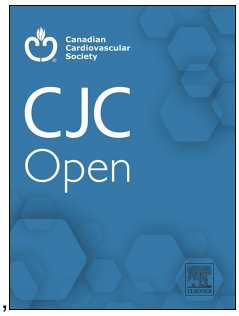

Canadian WATCHMAN Registry for Percutaneous Left Atrial Appendage Closure

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Canadian WATCHMAN Registry for Percutaneous Left Atrial Appendage Closure

Brief title: Canadian WATCHMAN Registry

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Abstract (250 words)

Background: Access to left atrial appendage closure (LAAC) in Canada is limited due to funding restrictions. This work aimed to assess Canadian clinical practice on patient selection, post-procedural antithrombotic therapy, and safety and/or efficacy with WATCHMAN implantation.

Methods: Seven Canadian centers implanting WATCHMAN participated in this prospective multicenter, observational registry. All procedures were done under general anesthesia with transesophageal echocardiography guidance. Patients were prospectively followed for 2years. Long-term stroke rate was compared with the expected rate based on CHA_2DS_2-VASc score.

Results: A total of 272 patients who underwent WATCHMAN LAAC between December 2013 and August 2019 (mean age [SD]: 75.4 [8.75] years; male, 63.2%; CHA_2DS_2-VASc: 4.35 [1.64]; HAS-BLED: 3.55 [0.94]) were included. Most patients (90.4%) had prior history of bleeding (80.5% major, 21.7% minor). The WATCHMAN device was successfully implanted in 269 patients (98.9%), with a few procedure-related complications including 5 pericardial effusions requiring drainage (1.8%) and 1 death (0.4%; 22 days post-LAAC from respiratory failure). Post-LAAC antithrombotic therapy included dual antiplatelet therapy in 70.6%, single antiplatelet therapy 18.4%, and OAC 13.6%. During the follow-up period (mean 709.7 [467.2] days), there was 81.4% reduction of ischemic stroke rate based on the expected rate from CHA_2DS_2-VASc score (6.0% expected vs. 1.1% observed). Device-related thrombus was detected in 1.8%.

Conclusion: The majority of Canadian patients who underwent LAAC had OAC contraindication due to prior bleeding, and most were safely treated with antiplatelet therapy post-LAAC with low device-related thrombus incidence. Long-term follow-up demonstrated that LAAC achieved a significant reduction in ischemic stroke rate.

Key words: left atrial appendage closure; atrial fibrillation; Watchman; stroke; Canada

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a major cause of stroke, responsible for 15% of all strokes and 30% of strokes in patients age>80.(1) Importantly, strokes associated with AF are more severe; AF-related stroke victims have 50% greater likelihood to become disabled, and >50% likelihood of death.(2,3) Accordingly, stroke prevention is one of the main pillars of AF management; the Canadian Cardiovascular Society recommends anticoagulation for most patients with age 65 years or older or $CHADS_2$ score ≥ 1 and the European Society of Cardiology recommends anticoagulation for CHA_2DS_2-Vasc≥1.(4,5)

The benefit of OAC in stroke prevention has to be balanced with the risk of major bleeding. Despite the safety profile of non-vitamin K oral anticoagulation (NOAC), the annual incidence of major bleeding ranges from 2.13% to 3.6%, with an annual incidence of intracranial hemorrhage ranging from 0.1% to 0.5%.(6-8) Therefore, even though OAC is effective for thromboembolic prevention, there remain a large proportion of eligible patients not on therapy for multiple reasons. These challenges have led to the investigations of device-based therapies for non-valvular AF including percutaneous left atrial appendage closure (LAAC) to prevent stroke, which is a major source of thrombus related to AF. Randomized controlled trials (PROTECT-AF & PREVAIL) have shown safety and efficacy of the WATCHMAN device in comparison to warfarin in patients eligible for OAC.(9-11) Among patients with contraindications to OAC, randomized trials comparing LAAC to antiplatelet/no therapy are ongoing, but enrolment rates have been very slow, and the ASAP-TOO trial

was stopped prematurely due to recruitment challenge.(12) Nevertheless, based on cumulative evidence, LAAC is given a class IIB recommendation for patients with high stroke-risk and contraindications to long-term OAC.(5)

Despite accumulating data, access to LAAC in Canada is limited due to funding restrictions. We aimed to assess the early Canadian clinical experience with LAAC, assessing patient selection, procedural outcomes, post-procedural antithrombotic therapy, and the safety and long-term efficacy with WATCHMAN implantation.

Methods

The Canadian WATCHMAN Registry is a multicenter prospective, non-randomized, observational registry enrolling consecutive patients undergoing LAAC with the WATCHMAN legacy device in Canadian cardiac catheterization or electrophysiological laboratories. All Canadian centers implanting WATCHMAN were invited to participate in this multicenter registry; 7 of 11 sites participated. Institutional research ethics boards approvals were obtained and patients gave informed consents for prospective follow-up.

Patient Population

Patients with non-valvular AF (paroxysmal, persistent or permanent) who met the following inclusion and exclusion criteria were included. Inclusion criteria included 1) age ≥18 years, and 2) $CHADS_2$ ≥1

and/or CHA_2DS_2-Vasc ≥2, and 3) prior major bleeding (intracranial, gastrointestinal bleeding, intraocular, respiratory, genitourinary, retroperitoneal, pericardial, anemia requiring transfusions, etc.), or contraindications to long-term OAC (HASBLED ≥3, high fall risk, cerebral aneurysm, blood dyscrasias, aortic dissection, renal failure, etc.), or failure of OAC (stroke/TIA while on OAC), or patients deemed not suitable for long-term anticoagulation. Patients with the presence of LAA thrombus or severe untreated mitral stenosis were excluded.

Pre-procedure imaging

Pre-procedural baseline transesopageal echocardiography (TEE) was routinely recommended, or alternatively, cardiac computed tomography angiography (CCTA) was performed instead of TEE pre-procedure, to rule out pre-existing LAA thrombus and to evaluate LAA anatomy and dimensions for accurate measurement of the widest LAA ostium (usually at the level of the circumflex artery) at 0, 45, 90, and 135 degrees, and also the available depth of the LAA (from ostium to apex of LAA).

Procedural details

All procedures were done under general anesthesia with TEE guidance. Intravenous heparin was administered pre- or immediately following transseptal puncture to maintain activated clotting time >250-300s during the procedure. To ensure adequate mean left atrial pressure (>12mmHg) for more accurate LAA measurements, saline bolus was administered if necessary. Device sizing selection was

based upon the maximum LAA ostium diameter. Oversizing was recommended by 9-25% based on the widest LAA measurement. Before device release, fulfillment of 4 criteria (PASS) was confirmed: (1) Position (device distal or at the ostium of the LAA; protrusion of shoulder by <5-7mm was acceptable), (2) Anchor (testing stability by retracting the deployment knob and letting go, to assess return to original position), (3) Size (device shoulder compressed 8-20% of original size on TEE) (table 2), and (4) Seal (assess TEE for any residual flow; must be <5mm before release). When all criteria were met, the device was released. Final angiography and TEE assessment were then performed.

Post-procedure dual antiplatelet therapy (DAPT) with aspirin 81mg/d and clopidogrel 75mg/d is commonly recommended for 3 months and followed by life-long aspirin alone; however, the post-LAAC antithrombotic regimen was at physician discretion. Post-procedural imaging with TEE or CCTA were recommended 1-6 months post-LAA closure.

Clinical follow-up

Long-term events (stroke, transient ischemic attack [TIA], systemic embolism [SE], cardiovascular [CV] death, non-CV death, major bleeding, and minor bleeding) were collected prospectively. Clinical or telephone follow-up were obtained at 3, 12 and 24 months post-LAAC.

Definitions

Procedural major adverse events (MAE) were defined as a composite of death, device embolization, stroke, SE, myocardial infarction, cardiac tamponade, and major bleeding. Other procedural complications (pericardial effusion not requiring drainage and minor bleeding) were also assessed. For long-term follow-up, major adverse cardiovascular events (MACE), defined as a composite of death, stroke, TIA, SE, and MI, were assessed. In addition, major and minor bleeding was also evaluated. For patients who underwent device surveillance (CCTA or TEE), the incidence of device-related thrombus (DRT) and peri-device leak (PDL) was assessed. The definition of DRT and PDL was in accordance with previous studies.(13)

Statistical analysis

For continuous variables, means and standard deviations were calculated and compared using the Wilcoxon test. Binary variables are reported as counts and percentages and between-group differences were assessed using the $\chi 2$ test. The efficacy of WATCHMAN in preventing stroke, TIA, and systemic embolism was tested by comparing the observed event-rate at follow-up with the predicted event-rate by the $CHADS_2$ and CHA_2DS_2-Vasc scores (1). The average annual risk for the whole study population was calculated from the predicted individual patient annual risk. The observed annualized ischemic stroke rate and thromboembolic event-rate (stroke, TIA, and SE) were subtracted from the predicted event-rates, and divided by the predicted event-rate x100, to obtain the % relative risk reduction (% relative reduction).

Data were analyzed using R software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). All p values were 2-sided, and significance was defined as $p<0.05$ for all analyses.

Results

Baseline Characteristics

A total of 272 patients (mean age [SD]: 75.4 [8.8] years; male, 63.2%; CHA_2DS_2-VASc: 4.4 [1.6]; HAS-BLED: 3.6 [0.9]) were enrolled in the Canadian Watchman Registry between December 2013 and August 2019 from 7 Canadian centers (**Table 1**): 140 cases were performed in Vancouver, 41 in Laval, 37 in Saskatoon, 32 in Regina, 11 in Montreal, 9 in Winnipeg, and 2 in Calgary. About 1/3 of patients had a history of stroke (29.4%), TIA (14.7%), and systemic embolization (4.0%). Only 5.1% of patients underwent prior catheter ablation for AF. Most patients (90.4%) had prior history of bleeding (80.5% major, 21.7% minor).

Procedural Details and In-hospital Outcomes

Almost all patients (95.2%) were evaluated by preprocedural TEE, and CTA was performed for 58.8% of patients prior to LAAC. The WATCHMAN device was successfully implanted in 269 patients (98.9%) (**Table 2**). Mean total procedure time was 89.1 (31.9) minutes and length of hospital stay was 1.6 (3.3) days. MAE was confirmed in 3.3% of patients including 5 pericardial effusions requiring drainage (1.8%) and 1 death (0.4%; 22 days post-LAAC from respiratory failure) (**Table 3**). There

were 6 (2.2%) mild pericardial effusions that did not require intervention. Post-LAAC antithrombotic agents included DAPT in 70.6%, single antiplatelet therapy (SAPT) 18.4%, and OAC 13.6% (**Table 4**).

Long-term Clinical Outcomes

During the follow-up period (mean 709.7 [467.2] days), MACE was confirmed in 16.5% of patients (including 3.7% stroke and 1.5% TIA) (**Table 5**). A total of 31 patients died during follow-up and 67.7% were non-cardiovascular reasons. Bleeding events occurred in 19.1% of patients who underwent LAAC during follow-up (8.8% major bleeding, 10.3% minor bleeding); 9 (1.9%) cases of major bleeding occurred within 3 months post-procedure. Follow-up device surveillance (either TEE or CTA; at mean 103 [115] days post-procedure) was performed in most patients (84.2%) and DRT was detected in 5 patients (1.8%) and the severe PDL (>5mm) was confirmed in 3 cases (1.1%).

There was 81.4% and 73.8% reduction of ischemic stroke rate, and a composite of ischemic stroke, TIA, and systemic embolization rate, respectively, based on the expected rate from CHA_2DS_2-VASc score (ischemic stroke: 6.0% expected vs. 1.1% observed; composite of ischemic stroke, TIA, and systemic embolization: 8.4% vs. 2.2%) (**Figure 1**). When stratified by antithrombotic strategy at the time of discharge, the rates of MACE, DRT, bleeding event, and any PDL were not different (**Figure 2**).

Discussion

In this largest Canadian prospectively registry of patients undergoing LAAC with the WATCHMAN device to-date, we found that (a) >1/3 of patients had a history of cerebrovascular disease and >90% had a prior history of bleeding events, (b) the WATCHMAN device was successfully implanted in the majority of cases (98.9%) with 3.3% peri-procedural MAE including 5 pericardial effusions requiring drainage (1.8%) and 1 death due to respiratory failure (0.4%), (c) DAPT was the predominant antithrombotic regimen after LAAC (70.6%) and OAC was used only in 18.4%, and (d) the follow-up data showed a 81.4% reduction of ischemic stroke rate based on the expected rate from CHA_2DS_2-VASc score (6.0% expected vs. 1.1% observed).

This study cohort comprises the early Canadian experience with the WATCHMAN legacy device. Health Canada approved the WATCHMAN device in Jan 2016, and prior to this time period, implant of WATCHMAN was under the special access program. Thus, patient selection for this procedure was rigorous and restricted, and a high proportion of our patients had prior bleeding events (90.4%), with most having had major bleeding (>1/3 had prior intracranial bleeding). The National Cardiovascular Data Registry LAAO Registry, a prospective, nationwide registry designed to function as the formal post-market surveillance in the US, enrolled patients undergoing LAAC with WATCHMAN during a similar timeframe (between January 2016 and December 2018), and showed lower proportions of prior major bleeding and intracranial bleeding (69.5% vs. 80.5%, and 11.9% vs. 36.4%, respectively) compared to our Canadian cohort.(14) This disparity is largely due to the stricter

indication for LAAC in Canada due to funding restrictions, where percutaneous LAAC is generally performed in patients with high stroke-risk and absolute/relative contraindications to OAC or failure on OAC. There is yet to be published randomized trial data on LAAC in patients contraindicated to OAC. The ASAP-TOO study was stopped prematurely,(15) while the STROKE-CLOSE (NCT02830152) and CLOSURE-AF (NCT03463317) studies are ongoing but enrolment rates are slow. Thus, real-world registries evaluating the effectiveness and safety of LAAC in patients contraindicated to OAC remain highly relevant in the current era. There are also ongoing large, randomized trials comparing LAAC versus NOACs in AF patients suitable for OAC (e.g. the CHAMPION-AF (NCT04394546) and CATALYST (NCT04226547) trials), which may expand the indications for LAAC in Canada in the near future.

The technical success rate with this device in our study was 98.9%, which was higher than that of pivotal trials such as PROTECT-AF and PREVAIL,(9,10) and compatible with recent registries.(16,17) The rate of in-hospital adverse events in our registry was also compatible with that of pivotal trials and other registries, (9,10,17,18) with the most frequent peri-procedure complications being cardiac tamponade requiring drainage. The improved implant success rate of recent registries including our study is attributed to increasing operator experience and likely complimented by the use of pre-procedure CT assessment. A learning curve phenomenon was previously described with LAAC, and 30 cases was proposed as a threshold to reach proficiency and to optimize clinical outcomes.(19) Similar to other structural heart disease interventions, CT assessment has been widely used as a pre-

procedure evaluation and can provide accurate LAA morphology and sizing.(20) The next-generation WATCHMAN FLX device is now commercially available, and early studies have shown this new device to be associated with a lower incidence of adverse events and high incidence of effective appendage closure.(21)

In the Canadian WATCHMAN Registry, the majority of patients were managed with antiplatelet therapy rather than anticoagulation therapy. In most patients (>70%), DAPT was prescribed and de-escalated to single antiplatelet therapy (SAPT) at the time of 1-6 months after the procedure. In selected patients with a very high-risk for bleeding (~10%), SAPT was the initial antithrombotic regimen post-LAAC. In contrast, in the early US experience with the WATCHMAN legacy device, >90% of patients undergoing LAAC were discharged home on OACs with either warfarin or NOAC.(14) Despite the significant difference in antithrombotic regimen, the incidence of ischemic stroke in our cohort was 3.7% during the mean 2yr follow-up, which was comparable to that in the US cohort (1.4% during 1-year follow-up). Importantly, the rate of major bleeding in our study cohort was lower than that in the US cohort (8.8% for mean 2-year follow-up vs. 7.9% for 1-year follow-up).(14) In addition, >80% of patients underwent post-implant surveillance using either CT or TEE, and DRT was detected only in 1.8%, which appeared lower than previously reported (3.8%).(22) Given the lower bleeding event with similar efficacy to prevent ischemic events and DRT, our data suggests that an antiplatelet-dominant antithrombotic strategy post-LAAC is safe. Further investigation is warranted to assess the optimal antithrombotic regimen.

Limitations

There are several limitations in our study. Our Canadian WATCHMAN Registry included 7 of 11 sites performing LAAC in Canada, thus, we did not enroll all WATCHMAN cases performed in Canada during the time period. Nevertheless, we believe our registry was representative of the clinical practice, patient selection, and outcomes of real-world LAAC in Canada. This is an observational registry; thus the use of pre-procedural imaging, device surveillance post-procedure, and use of antithrombotic regimen was at the discretion of the physicians. Although the clinical data were prospectively collected by each center, the events and imaging results were not adjudicated. The new-generation WATCHMAN FLX device has now largely replaced the WATCHMAN legacy device. Given the excellent performance of WATCHMAN FLX as reported in the PINNACLE Registry,(21) its implementation may influence safety and effectiveness, but this new device was not evaluated in our cohort.

Conclusions

The majority of Canadian patients who underwent WATCHMAN LAAC had OAC contraindication due to prior bleeding, and most were safely treated with antiplatelet therapy post-LAAC with low DRT incidence. LAAC procedural complications were low, and the follow-up observed ischemic stroke rate was lower than the predicted rate based on the $CHADS_2$ and CHA_2DS_2-Vasc scores. In the absence of

published randomized trial data, our registry findings support the use of WATCHMAN LAAC in patients with contraindications to OAC. Further investigations are warranted to investigate new device iterations and the optimal antithrombotic regimen post-LAAC for patients contraindicated to OAC.

DISCLOSURES

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Table 1. Baseline Characteristics

Baseline Characteristics	N=272
Age (mean (SD)), years	75.36 (8.75)
Male, n (%)	172 (63.2)
Body mass weight (mean (SD)), kg/m2	28.19 (6.02)
Atrial fibrillation type	
Permanent or persistent, n (%)	153 (56.2)
Paroxysmal, n (%)	118 (43.4)
Unknown, n (%)	1 (0.4)
History of LAA thrombus, n (%)	13 (4.8)
Hypertension, n (%)	203 (74.6)
Dyslipidemia, n (%)	176 (64.7)
Diabetes, n (%)	90 (33.1)
Smoking history	
Current smoker, n (%)	22 (8.1)
Former smoker, n (%)	120 (44.1)
Coronary artery disease, n (%)	104 (38.2)
Prior percutaneous coronary intervention, n (%)	54 (19.9)
Coronary artery bypass grafting, n (%)	40 (14.7)
Chronic heart failure, n (%)	70 (25.7)
Left ventricular ejection fraction <40%, n (%)	53 (19.5)
Prior valve surgery, n (%)	21 (7.7)
Prior stroke, n (%)	80 (29.4)
Prior transient ischemic attack, n (%)	40 (14.7)
Prior systemic embolization, n (%)	11 (4.0)
Prior atrial fibrillation ablation, n (%)	14 (5.1)
Peripheral artery disease, n (%)	19 (7.0)
Pacemaker, n (%)	55 (20.2)
Intracardiac defibrillator, n (%)	11 (4.0)
Creatinine (mean (SD)), μmol/L	106.76 (46.59)
Laboratory data	
Estimated GFR (mean (SD)), mL/min/1.73m2	59.37 (20.06)
Hemoglobin baseline (mean (SD)), g/dL	125.26 (19.94)

Indications for LAA closure	
CHA_2DS_2-VASc (mean (SD))	4.35 (1.64)
HAS-BLED score (mean (SD))	3.55 (0.94)
Previous minor bleeding, n (%)	59 (21.7)
Previous major bleeding, n (%)	219 (80.5)
Intracranial, n (%)	99 (36.4)
Gastrointestinal, n (%)	106 (39.0)
Retroperitoneal, n (%)	4 (1.5)
Intraocular, n (%)	7 (2.6)
Respiratory, n (%)	6 (2.2)
Urogenital, n (%)	8 (2.9)

Abbreviations: SD, standardized difference; LAA, left atrial appendage; GFR, glomerular filtration rate

Table 2. Procedural Details

Procedural Details	N=272
Technical success, n (%)	269 (98.9)
Implanted WATCHMAN Size (%)	
21 mm	28 (10.3)
24 mm	48 (17.6)
27 mm	80 (29.4)
30 mm	63 (23.2)
33 mm	50 (18.4)
Failed implantation	3 (1.1)
Total procedural time (mean (SD)), min	89.12 (31.86)
Fluoroscopy time (mean (SD)), min	13.66 (8.39)
Total contrast (mean (SD)), ml	84.66 (52.30)
Length of hospital stay (mean (SD)), days	1.64 (3.32)
Number of devices attempted (mean (SD))	1.30 (0.60)
Baseline TEE performed, n (%)	259 (95.2)
LAA dimension by TEE (mean (SD)), mm	22.35 (3.96)
LAA depth by TEE (mean (SD)), mm	30.37 (6.43)
Baseline CTA performed, n (%)	160 (58.8)
LAA dimension by CCTA (mean (SD)), mm	25.09 (4.65)
LAA depth by CTA (mean (SD)), mm	30.47 (6.80)

Abbreviations: SD, standardized difference; TEE, transesophageal echocardiography; LAA, left atrial appendage; CTA, computed tomography angiography

Table 3. Procedural Complications

Procedural Complications	N=272
Major adverse event: MAE	9 (3.3)
Death	1 (0.4)
Stroke/TIA/Systemic Embolization	0 (0)
Myocardial infarction	1 (0.4)
Pericardial tamponade requiring drainage	5 (1.8)
Device embolization	0 (0)
Major bleeding	2 (0.7)
Other in-hospital complications	
Pericardial effusion (small, no drainage)	6 (2.2)
Minor bleed (e.g. hematoma)	9 (3.3)

Abbreviations: TIA, transient ischemic attack

Table 4. Discharge Antithrombotic Agents

Discharge Antithrombotic Agents	N=272
Aspirin	230 (84.6)
Clopidogrel	203 (74.6)
Ticagrelor	1 (0.4)
Warfarin	5 (1.8)
DOAC: direct oral anticoagulant	32 (11.8)
Antithrombotic Regimen	
DAPT: dual antiplatelet therapy	192 (70.6)
SAPT: single antiplatelet therapy	50 (18.4)
OAC: oral anticoagulant	37 (13.6)
None	6 (2.2)

Table 5. Adverse Events During Follow-up

Overall Events	N=272
Follow-up (mean (SD)), days	709.7 (467.2)
Composite death/stroke/TIA/MI, n (%)	45 (16.5)
Cardiovascular death, n (%)	10 (3.7)
Non-cardiovascular death, n (%)	21 (7.7)
Stroke, n (%)	10 (3.7)
TIA, n (%)	4 (1.5)
Systemic embolization, n (%)	0 (0)
Myocardial infarction, n (%)	2 (0.7)
Major bleeding, n (%)	24 (8.8)
Minor bleeding, n (%)	28 (10.3)
Device Surveillance (TEE or CTA), n (%)	229 (84.2)
Device-related thrombus, n (%)	5 (1.8)
Peri-device leak (on TEE) (N=216)	
Any leak, n (%)	76 (35.2)
Minimal <1mm, n (%)	27 (12.5)
Minor 1-3mm, n (%)	24 (11.1)
Moderate 3-5mm, n (%)	20 (9.3)
Severe >5mm, n (%)	3 (1.4)

Abbreviations: SD, standardized difference; TIA, transient ischemic attack; MI, myocardial infarction;

TEE, transesophageal echocardiography; CTA, computed tomography angiography

Figure 1. Observed/Expected Ratio for Thromboembolic Events Based on CHA_2DS_2-Vasc and $CHADS_2$ scores

Abbreviations: TIA, transient ischemic attack; SE, systemic embolization; %RR, percent relative reduction

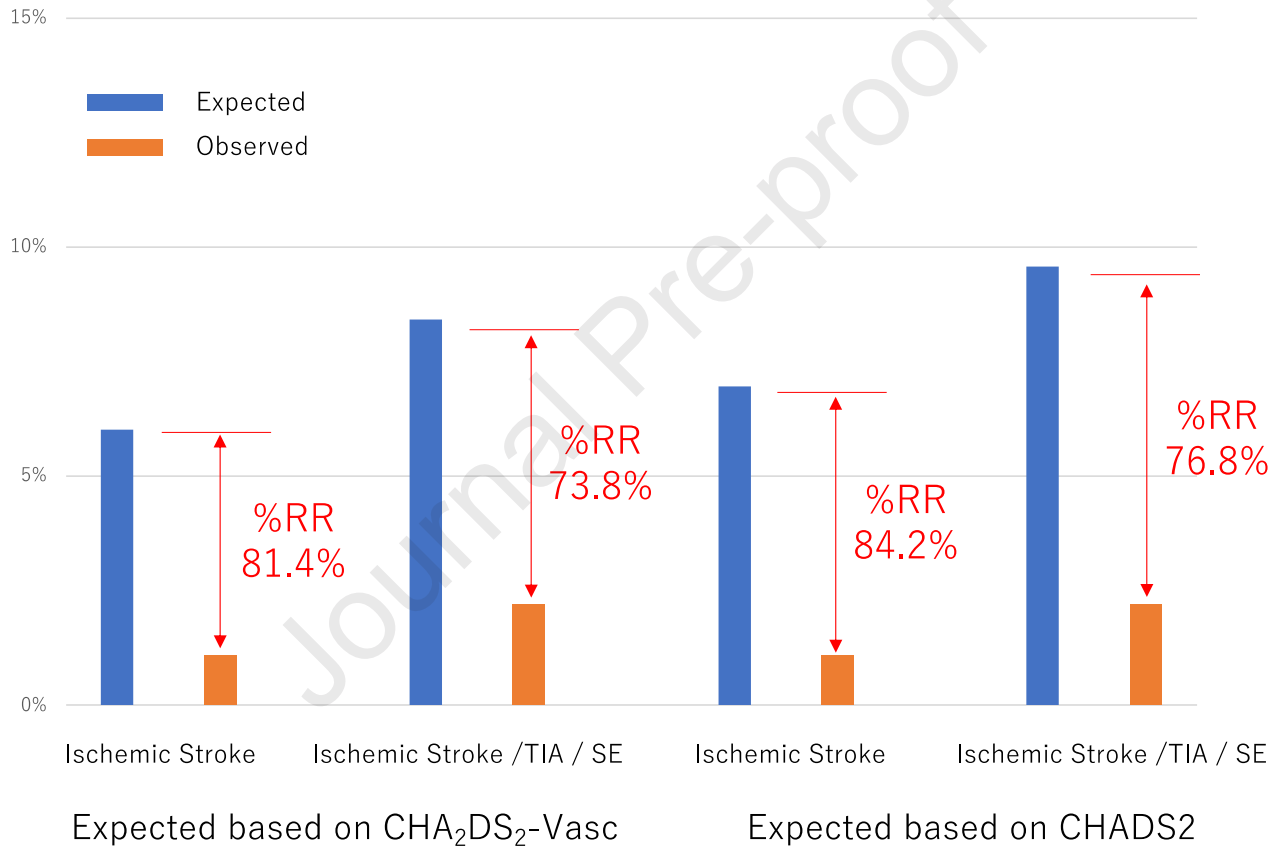

Figure 2. Adverse Events During Follow-up by Antithrombotic Strategy

Abbreviations: DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; OAC, oral anticoagulant; TIA, transient ischemic attack; MI, myocardial infarction; DRT, device-related thrombus