Introduction

Underutilization of oral anticoagulation therapy for stroke prevention in patients with CHA2DS2-VASc score $\geq 2$ and atrial fibrillation (AF) represents a major unmet clinical need.\(^1\) Left atrial appendage closure (LAAC) is a viable strategy for stroke risk reduction in patients with nonvalvular AF who can tolerate systemic oral anticoagulation therapy but are poor candidates for long-term anticoagulation.\(^2,3\) The
Watchman 2.5 generation device (Boston Scientific Inc., Marlborough, MA) for LAAC reduces the risk of stroke in select patients on the basis of the results of the PROTECT-AF and PREVAIL randomized trials.\textsuperscript{4,5} Implant success after randomization was 90.9\% in PROTECT-AF and 95.1\% in PREVAIL with improved training protocols.\textsuperscript{4,6}

A 95\% closure rate persists in real-world registries despite the use of preprocedure imaging to exclude patients with prohibitive left atrial appendage (LAA) anatomy such as inadequate LAA depth (instructions for use state that the LAA depth must be at least as long as the LAA ostium width).\textsuperscript{7,8} Limitations of the device size matrix (device size 21, 24, 27, 30, and 33 mm requiring 17–31 mm LAA ostial width), recapture risk of intraprocedural perforation (1\%–2\%), device-related thrombus formation 3\%–4\%, and peridevice leak 2\%–10\%, all reduce the potential net clinical benefit of LAAC.\textsuperscript{9} Small case series and cohort studies support the feasibility of using Watchman 2.5 for very small ostia <17 mm or in failed surgical LAA ligation with narrow necks, whereas cases with ostia >31 mm would be at high risk for device embolization.\textsuperscript{10,11} Anterior chicken wing anatomy often poses an anatomic challenge to LAAC regardless of width with an increased risk of pericardial effusion and cardiac perforation.\textsuperscript{12}

The Watchman FLX device is a self-expanding nitinol frame with a permeable polyester fabric covering the atrial facing surface and 18 peripheral fixation anchors in 2 layers designed to improve stability and reduce embolization risk in comparison to the Watchman 2.5 device. The FLX device is available in 20, 24, 27, 31, and 35 mm sizes (range of suitable implant diameter 14–31.5 mm). The closed distal end allows full recapture and redeployment, reducing the risk of perforation particularly relevant in cases with challenging LAA anatomy or restrictive depth. The length of the device was reduced, so the LAA is only required to be half the depth compared with the ostia width for an implant (eg, 24 mm FLX device being placed in a 20 mm ostial LAA width would need only 10 mm implant depth).

The PINNACLE FLX study evaluated the safety and efficacy of the Watchman FLX device in patients with non-valvular AF. The primary safety end point in 400 subjects was met with major procedural risk at 0.5\% (performance goal 4.21\%) and the primary efficacy end point met with 100\% LAA seal (performance goal of 97.0\% for closure with any leak <5 mm; \( P < .0001 \)).\textsuperscript{13} We hypothesized that a large proportion of patients enrolled in the single-arm PINNACLE FLX trial were held back specifically by implanting physicians for Watchman FLX on the basis of previously failed attempts at a Watchman 2.5 device or on the basis of prohibitive LAA anatomy as assessed by preprocedural tranesophageal echocardiography (TEE) or computed tomography, raising safety concerns for an attempt using the Watchman 2.5 device.

Methods

The roll-in (n = 58) and primary effectiveness (n = 400) cohort of the prospective investigational device exemption (IDE) trial for the Watchman FLX device comprised the study population. PINNACLE FLX was sponsored by Boston Scientific Corporation (Marlborough, MA) and registered at www.clinicaltrials.gov under the identifier NCT02702271. All study participants signed informed consent before enrollment, and the study protocol was approved by institutional review boards at the study sites. The research reported in this article adhered to ethics guidelines as outlined in the revised Helsinki Declaration 2013.

Subjects from the IDE cohort were identified who had previously undergone a failed attempt at LAAC with Watchman 2.5 (n = 11) or who were excluded from Watchman 2.5 eligibility primarily on the basis of core laboratory LAA dimensions on TEE (<17 or >31 mm maximum ostial width and/ or depth less than half of the maximum LAA width) or cardiac computed tomographic angiography (CTA) anatomy, similarly indicating probable failure to implant Watchman 2.5 as reported by the study sites (n = 88). Demographic characteristics, implant procedure details, and TEE follow-up data were compared to a control group composed of PINNACLE FLX enrollees who did not meet these criteria (n = 359).

The primary effectiveness end point was the rate of effective LAAC, defined as any peridevice flow with jet size \( \leq 5 \) mm per core laboratory–assessed TEE at 12 months. Clinical outcomes as of January 2020 are reported in this article. Descriptive statistics are provided for subject demographic and baseline characteristics, procedural characteristics, and medication compliance. The rates of major clinical events, device- or procedure-related serious adverse events, and rates of LAAC are also provided. Time-to-event outcomes are summarized using Kaplan-Meier estimates, with 95\% confidence intervals calculated using log-log methodology. Statistical comparisons between the study and control cohorts are based on the Student \( t \) test (continuous parameters), Fisher exact test (categorical parameters), and log-rank test (time-to-event outcomes). Nominal \( P \) values are reported, and there are no adjustments for multiple comparisons. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

The PINNACLE FLX study enrolled 58 roll-in subjects and 400 primary study subjects between May 2018 and November 2018. Subjects with a prior failed Watchman 2.5 attempt (n = 11 [2.4\%]) or prohibitive anatomy to attempt LAAC with Watchman 2.5 (n = 88 [19.2\%]) are defined as the “study cohorts” and represented 21.6\% of all Watchman FLX patients (99 of 458) in the PINNACLE FLX IDE trial. Implant procedure success, defined as the successful delivery and release of a stable device into the LAA, was achieved in 96 of 99 patients (97.0\%) in the study cohorts and in 356 of 359 (99.2\%) in the control cohort (\( P = .85 \)). The prohibitive anatomy cohort mainly reflected very small LAA ostia <17 mm (n = 51) or restricted depth for implant with the lowest ratio of depth to width of 0.6 (n = 37). No patients were attempted with LAA ostium width >31 mm.
### Table 1 Baseline patient data

| Parameter                        | Failed WM 2.5 cohort (n = 11) | Prohibitive anatomy cohort (n = 88) | Control cohort (n = 359) | $P^*$: failed WM 2.5 vs control | $P^*$: prohibitive anatomy vs control |
|----------------------------------|-------------------------------|------------------------------------|--------------------------|-------------------------------|-------------------------------------|
| Age (y)                          | 78.6 ± 6.3 (11)               | 73.3 ± 8.4 (88)                    | 74.0 ± 8.7 (359)         | .08                           | .49                                 |
| Sex: male                        | 72.7 (8/11)                   | 64.8 (57/88)                       | 63.2 (227/359)           | .75                           | .81                                 |
| Roll-in case                     | 9.1 (1/11)                    | 11.4 (10/88)                       | 13.1 (47/359)            | >.99                          | .73                                 |
| Race/ethnicity                   |                               |                                    |                          |                               |                                     |
| Asian                            | 0.0 (0/10)                    | 1.2 (1/85)                         | 0.3 (1/340)              | >.99                          | .36                                 |
| Black or African heritage        | 0.0 (0/10)                    | 1.2 (1/85)                         | 5.6 (19/340)             | >.99                          | .15                                 |
| Caucasian                        | 100.0 (10/10)                 | 95.3 (81/85)                       | 93.5 (318/340)           | >.99                          | .80                                 |
| Hispanic or Latino               | 0.0 (0/10)                    | 5.9 (5/85)                         | 1.5 (5/340)              | >.99                          | .03                                 |
| CHADS$_2$-VASC score             | 4.6 ± 2.1 (11)                | 4.0 ± 1.5 (88)                     | 4.3 ± 1.5 (359)          | .42                           | .15                                 |
| CAD with prior stent (DES or other) | 27.3 (3/11)               | 13.6 (12/88)                       | 18.7 (67/359)            | .44                           | .35                                 |
| CAD with prior CABG              | 9.1 (1/11)                    | 9.1 (8/88)                         | 11.4 (41/359)            | >.99                          | .70                                 |
| Hypertension                     | 81.8 (9/11)                   | 84.1 (74/88)                       | 85.5 (307/359)           | .67                           | .74                                 |
| Congestive heart failure or left ventricular dysfunction | 9.1 (1/11) | 17.0 (15/88) | 30.4 (109/359) | .19 | .01 |
| Mitral valve regurgitation       | 72.7 (8/11)                   | 65.9 (58/88)                       | 75.2 (270/359)           | >.99                          | .08                                 |
| Carotid artery disease           | 9.1 (1/11)                    | 10.2 (9/88)                        | 9.7 (35/359)             | >.99                          | .84                                 |
| Previous TIA                     | 0.0 (0/11)                    | 13.6 (12/88)                       | 7.5 (27/359)             | >.99                          | .09                                 |
| Previous stroke                  | 36.4 (4/11)                   | 13.6 (12/88)                       | 17.0 (61/359)            | .11                           | .52                                 |
| Previous hemorrhagic stroke      | 18.2 (2/11)                   | 1.1 (1/88)                         | 6.4 (23/359)             | .17                           | .06                                 |
| AF pattern                       |                               |                                    |                          |                               |                                     |
| Paroxysmal AF                    | 27.3 (3/11)                   | 60.2 (53/88)                       | 49.9 (179/359)           | .22                           | .095                                |
| Persistent AF                    | 27.3 (3/11)                   | 22.7 (20/88)                       | 40.4 (145/359)           | .54                           | .002                                |
| Permanent AF                     | 45.5 (5/11)                   | 15.9 (14/88)                       | 8.1 (29/359)             | .002                          | .04                                 |
| Paced AF                         | 0.0 (0/11)                    | 1.1 (1/88)                         | 1.7 (6/359)              | >.99                          | >.99                                |

Values are presented as mean ± SD (n) or % (n/total n).

$P^*$ values are based on the Student $t$ test. For categorical parameters, $P$ values are based on the Fisher exact test.

### Table 2 Transesophageal echocardiography at baseline and implant

| Parameter                        | Failed WM 2.5 cohort (n = 11) | Prohibitive anatomy cohort (n = 88) | Control cohort (n = 359) | $P^*$: failed WM 2.5 vs control | $P^*$: prohibitive anatomy vs control |
|----------------------------------|-------------------------------|------------------------------------|--------------------------|-------------------------------|-------------------------------------|
| Baseline data                    |                               |                                    |                          |                               |                                     |
| LVEF (%)                         | 53.5 ± 3.5 (11)               | 58.0 ± 8.5 (88)                    | 55.7 ± 8.4 (359)         | .38                           | .02                                 |
| Presenting in sinus              | 27.3 (3/11)                   | 58.0 (51/88)                       | 59.1 (212/359)           | .06                           | .90                                 |
| Presenting in AF or atrial flutter | 72.7 (8/11)               | 25.0 (22/88)                       | 30.1 (108/359)           | .005                          | .36                                 |
| Mitral valve regurgitation (moderate or severe) | 14.3 (1/7) | 4.0 (3/75) | 6.0 (18/299) | .36 | .78 |
| Pericardial effusion             | 0.0 (0/9)                     | 1.1 (1/87)                         | 1.7 (6/346)              | >.99                          | >.99                                |
| LAA ostium diameter (mm)         | 22.7 ± 4.0 (9)                | 18.1 ± 4.2 (88)                    | 20.4 ± 3.1 (347)         | .03                           | <.001                               |
| LAA length (mm)                  | 27.9 ± 5.9 (9)                | 23.9 ± 5.3 (88)                    | 28.8 ± 5.6 (347)         | .61                           | <.001                               |
| Number of LAA lobes              | 1.2 ± 0.4 (9)                 | 1.2 ± 0.4 (87)                     | 1.1 ± 0.3 (348)          | .45                           | .37                                 |
| Any evidence of SEC              | 25.0 (2/8)                    | 13.8 (12/87)                       | 20.5 (71/346)            | .67                           | .17                                 |
| Evidence of sludge, dense SEC, or LAA thrombus | 0.0 (0/9) | 0.0 (0/88) | 4.3 (15/349) | >.99 | .049 |
| Implant data                     |                               |                                    |                          |                               |                                     |
| Presenting in sinus              | 27.3 (3/11)                   | 58.0 (51/88)                       | 59.1 (212/359)           | .06                           | .90                                 |
| Presenting in AF or atrial flutter | 72.7 (8/11)               | 25.0 (22/88)                       | 30.1 (108/359)           | .005                          | .36                                 |
| Pericardial effusion             | 0.0 (0/10)                    | 1.1 (1/87)                         | 1.1 (4/348)              | >.99                          | >.99                                |
| LAA ostium diameter (mm)         | 22.7 ± 4.0 (9)                | 18.0 ± 4.0 (87)                    | 20.4 ± 3.1 (346)         | .03                           | <.001                               |
| LAA length (mm)                  | 27.9 ± 5.9 (9)                | 23.7 ± 5.1 (87)                    | 28.9 ± 5.4 (346)         | .57                           | <.001                               |
| Any evidence of SEC              | 22.2 (2/9)                    | 16.3 (14/86)                       | 18.4 (63/343)            | .67                           | .75                                 |
| Evidence of sludge, dense SEC, or LAA thrombus | 0.0 (0/10) | 0.0 (0/87) | 2.3 (8/346) | >.99 | .37 |
| Device spans the entire ostium   | 100.0 (10/10)                 | 94.1 (80/85)                       | 94.5 (327/346)           | >.99                          | .80                                 |

Values are presented as mean ± SD (n) or % (n/total n).

$AF = atrial fibrillation; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; SEC = spontaneous echo contrast; WM = Watchman.

$^*$For continuous parameters, $P$ values are based on the Student $t$ test. For categorical parameters, $P$ values are based on the Fisher exact test.
Three subjects in the prohibitive anatomy group could not be implanted with FLX (device implant success in 85 of 88 [96.6%]; \( P = .10 \) vs controls). The most common reason for an unsuccessful attempt across PINNACLE FLX subjects was unsuitable patient anatomy in 4 of 6 patients (eg, because of excessive vascular tortuosity, inadequate positioning, or insufficient anchoring). The remaining 2 unsuccessful attempts were due to not meeting device release criteria, specifically inadequate compression and seal.

Successful LAAC was performed with Watchman FLX in all subjects attempted who had a prior failed Watchman 2.5 attempt (11 of 11 [100%]). There was no difference in age, sex, CHA2DS2-VASc score, or HAS-BLED score between either study populations or the control cohort (see Table 1). The mean age of the prohibitive anatomy cohort was 8.4 years, with 64.8% male subjects, mostly white (95.3%). Patients in the prohibitive anatomy cohort had a lower probability of systolic heart failure (17.0% vs 30.4%; \( P = .01 \)) and a slightly higher reported left ventricular ejection fraction (LVEF) (58.0% ± 8.5% vs 55.7% ± 8.4%; \( P = .02 \)). Contrast use, fluoroscopy time, total procedure time, and use of the smallest available device (20 mm) were significantly higher in the prohibitive anatomy cohort. Of the 51 subjects with <17 mm maximum LAA ostial width, 32 were implanted with a 20 mm Watchman FLX device and 19 with a 24 mm FLX device (see Tables 2 and 3). Patients in the prohibitive anatomy cohort had a significantly smaller LAA ostium diameter and reduced LAA length than did controls (diameter 18.0 ± 4 mm vs 20.4 ± 3 mm; \( P = .001 \) and length 23.7 ± 5 mm vs 28.9 ± 5 mm; \( P = .001 \)). Figure 1 demonstrates a PINNACLE FLX patient with a previously failed Watchman 2.5 implant attempt with anterior chicken wing LAA anatomy. Figure 2 shows PINNACLE FLX patient with 31 mm ostial width broccoli LAA implanted with a 35 mm FLX device.

Patients with a previously failed attempt at Watchman 2.5 were more likely to be in permanent AF and had longer procedure times, more recaptures, and larger LAA diameter, resulting in greater use of the 35 mm Watchman FLX device (Table 3). Reasons for a prior failed attempt included anterior chicken wing LAA with inadequate depth (\( n = 3 \)), LAA ostium too large (>31 mm; \( n = 2 \)), LAA ostium too small (\( n = 1 \)), complications from the index Watchman 2.5 attempt (\( n = 1 \); 24 mm device embolization), or other LAA anatomy.

### Table 3  Implant procedural data

| Parameter                          | Failed WM 2.5 cohort (n = 11) | Prohibitive anatomy cohort (n = 88) | Control cohort (n = 359) | \( P^* \): failed WM 2.5 vs control | \( P^* \): prohibitive anatomy vs control |
|-----------------------------------|-------------------------------|-------------------------------------|--------------------------|-------------------------------------|------------------------------------------|
| Activated clotting time (s)       | 300.2 ± 78.4 (11)            | 288.5 ± 89.0 (87)                  | 300.0 ± 86.9 (358)       | >.99                                | .27                                       |
| Maximum left atrial pressure (mm Hg) | 14.1 ± 6.5 (11)              | 15.7 ± 5.7 (86)                    | 16.2 ± 16.8 (354)        | .68                                 | .82                                       |
| Volume of contrast used (mL)      | 59.6 ± 29.5 (11)             | 66.6 ± 43.1 (87)                   | 56.2 ± 40.0 (351)        | .77                                 | .03                                       |
| Procedure implant success         | 100.0 (11/11)                | 96.6 (85/88)                       | 99.2 (356/359)           | >.99                                | .09                                       |
| Procedure time (min)              | 52.2 ± 28.1 (11)             | 41.9 ± 23.4 (88)                   | 37.7 ± 20.8 (358)        | .02                                 | .09                                       |
| Total fluoroscopy time (min)      | 10.7 ± 6.5 (11)              | 10.7 ± 9.7 (88)                    | 7.5 ± 6.3 (357)          | .09                                 | <.001                                     |
| LAA diameter (mm)†                | 22.7 ± 4.0 (9)               | 18.0 ± 4.0 (87)                    | 20.4 ± 3.1 (346)         | .03                                 | <.001                                     |
| LAA length (mm)†                  | 27.9 ± 5.9 (9)               | 23.7 ± 5.1 (87)                    | 28.9 ± 5.4 (346)         | .57                                 | <.001                                     |
| LAA seal complete                 | 90.0 (9/10)                  | 92.7 (76/82)                       | 92.3 (313/339)           | .56                                 | >.99                                      |
| WATCHMAN FLX devices              |                               |                                     |                          |                                     |                                          |
| Number of implanted/attempted     | 1.1 ± 0.3 (11)               | 1.2 ± 0.4 (88)                     | 1.1 ± 0.3 (359)          | .68                                 | .006                                      |
| sheaths                           |                               |                                     |                          |                                     |                                          |
| Number of implanted/attempted     | 1.3 ± 0.5 (11)               | 1.2 ± 0.4 (88)                     | 1.2 ± 0.4 (359)          | .33                                 | .19                                       |
| WATCHMAN FLX devices              |                               |                                     |                          |                                     |                                          |
| 1 device attempted                | 72.7 (8/11)                  | 79.5 (70/88)                       | 86.6 (311/359)           | .18                                 | .10                                       |
| 2 devices attempted               | 27.3 (3/11)                  | 19.3 (17/88)                       | 12.0 (43/359)            | .14                                 | .08                                       |
| 3 devices attempted               | 0.0 (0/11)                   | 1.1 (1/88)                         | 1.1 (4/359)              | >.99                                | >.99                                      |
| Number of partial recaptures      | 2.1 ± 2.2 (11)               | 1.2 ± 1.8 (85)                     | 1.2 ± 1.6 (356)          | .05                                 | .91                                       |
| (implanted devices only)          |                               |                                     |                          |                                     |                                          |
| Number of full recaptures         | 0.4 ± 0.5 (11)               | 0.3 ± 0.8 (85)                     | 0.1 ± 0.5 (356)          | .10                                 | .006                                      |
| (implanted devices only)          |                               |                                     |                          |                                     |                                          |
| Final device size                 |                               |                                     |                          |                                     |                                          |
| 20 mm                             | 0.0 (0/11)                   | 37.6 (32/85)                       | 4.2 (15/356)             | >.99                                | <.001                                     |
| 24 mm                             | 18.2 (2/11)                  | 24.7 (21/85)                       | 25.8 (92/356)            | .74                                 | .89                                       |
| 27 mm                             | 18.2 (2/11)                  | 23.5 (20/85)                       | 35.4 (126/356)           | .34                                 | .04                                       |
| 31 mm                             | 36.4 (4/11)                  | 4.7 (4/85)                         | 27.2 (97/356)            | .50                                 | <.001                                     |
| 35 mm                             | 27.3 (3/11)                  | 9.4 (8/85)                         | 7.3 (26/356)             | .047                                | .50                                       |
| Final device size larger          | 33.3 (1/3)                   | 35.3 (6/17)                        | 46.7 (21/45)             | >.99                                | .57                                       |
| Final device size smaller         | 33.3 (1/3)                   | 35.3 (6/17)                        | 46.7 (21/45)             | >.99                                | .57                                       |
| Final device same as the first attempt | 33.3 (1/3)                   | 29.4 (5/17)                       | 6.7 (3/45)               | .23                                 | .03                                       |

Values are presented as mean ± SD (n) or % (n/total n).
LAA = left atrial appendage; WM = Watchman.
*For continuous parameters, \( P \) values are based on the Student t test. For categorical parameters, \( P \) values are based on the Fisher exact test.
†Core laboratory-reported data.
with usable LAA depth <17 mm (n = 4). Seven of the 11 subjects with a failed attempt were implanted with Watchman FLX by the same operator, 4 were referred to a study site specifically for an attempt with FLX (implants 1–12 months after a failed Watchman 2.5 attempt; median 3 months). There were no strokes, embolic events, or major bleeds in the interim.

The primary safety end point did not differ between the combined study cohort (at 1% [1 of 99]) and the control cohort (1 of 359 [0.3%]) (P = .84) (see Table 4). The all-cause death end point at 18 months was significantly lower in the prohibitive anatomy cohort (1.2% [1 of 88]) than in the control cohort (8.8% [29 of 359]) (P = .02). Additionally, cardiovascular mortality was lower in the prohibitive anatomy cohort than in the control cohort (0 of 88 [0%] vs 17 of 359 [4.7%]; P < .03) (see Figures 3 and 4). There were zero device embolizations in either cohort and 5 serious pericardial effusions (n = 5) in the control cohort vs zero in either of the study cohorts (n = 0). All patients with a significant pericardial effusion presented late (>7 days) after hospital discharge, were treated percutaneously, and were unrelated to intraoperative sheath or device perforation. There were no differences in stroke, transient ischemic attack, or major bleeding between groups.

Regarding primary effectiveness end points, at 45-day follow-up 100% (11 of 11 with a failed Watchman 2.5 attempt) and 96.5% (82 of 85 with prohibitive anatomy) of study cohort subjects with follow-up TEE discontinued anticoagulation because of adequate LAA seal (peridevice leak <5 mm) vs 96.3% (340 of 353) in the control cohort (P = .56). The study patients meeting the 12-month postimplant TEE criteria for adequate LAA seal with <5 mm peridevice leak were 94 of 94 in the combined study cohort (100%) and 305 of 305 in the control cohort (100%). A complete seal by TEE at 12-month postimplant with zero detectable peridevice leak was noted in 10 of 11 (90.9%) in the failed Watchman 2.5 cohort, 73 of 80 (91.3%) in the prohibitive anatomy cohort, and 273 of 305 in the control cohort (90.9%). Postimplant drug regimen selection heavily favored apixaban, with 10 of 11 in the failed Watchman 2.5 study cohort (90.9%), 67 of 85 (78.8%) in the prohibitive anatomy cohort, and 265 of 356 in the control cohort (74.4%) reporting use of apixaban for 45 days after Watchman FLX implantation. There was only 1 device-related thrombus in the combined study cohort (1 of 99 [1%]) vs 6 in the control group (6 of 359 [1.7%]) (P >.99).

**Discussion**

The currently available Watchman 2.5 LAAC device has reasonable safety and efficacy, and the major complication rate has improved with increasing physician experience (2%). The clinical effectiveness of Watchman 2.5 has reached a plateau when looking at the recently published NCDR Left Atrial Appendage Occlusion Registry data in

![Image](https://example.com/image.png)

**Figure 1** Anterior chicken wing left atrial appendage (LAA) prior attempt at Watchman 2.5 (A and B) as assessed by TEE and CTA at 1-year complete closure with 27 mm FLX (C and D). CTA = computed tomographic angiography; TEE = transesophageal echocardiography.
Figure 2  Large broccoli (28 mm × 31 mm) ostial width as assessed by CTA (A and B) implanted with a 35 mm FLX device (C and D). CTA = computed tomographic angiography.

Table 4  Major clinical events

| Parameter                                           | Failed WM 2.5 cohort (n = 11) | Prohibitive anatomy cohort (n = 88) | Control cohort (n = 359) | $P^*$: failed WM 2.5 vs control | $P^*$: prohibitive anatomy vs control |
|-----------------------------------------------------|-------------------------------|-------------------------------------|--------------------------|--------------------------------|-------------------------------------|
| All events through database snapshot                |                               |                                     |                          |                                 |                                     |
| All-cause death                                     | 9.1 (1/11)                    | 1.1 (1/88)                          | 8.1 (29/359)             | >.99                           | 0.02                               |
| Cardiovascular/unknown death                        | 0.0 (0/11)                    | 0.0 (0/88)                          | 4.7 (17/359)             | >.99                           | 0.03                               |
| TIA/stroke                                          | 9.1 (1/11)                    | 2.3 (2/88)                          | 3.3 (12/359)             | >.99                           | >0.99                              |
| TIA                                                 | 0.0 (0/11)                    | 0.0 (0/88)                          | 0.6 (2/359)              | >.99                           | >0.99                              |
| All stroke                                          | 9.1 (1/11)                    | 2.3 (2/88)                          | 2.8 (10/359)             | >.99                           | >0.99                              |
| Ischemic stroke                                     | 9.1 (1/11)                    | 2.3 (2/88)                          | 2.5 (9/359)              | >.99                           | >0.99                              |
| Hemorrhagic stroke                                  | 0.0 (0/11)                    | 0.0 (0/88)                          | 0.3 (1/359)              | >.99                           | >0.99                              |
| Systemic embolism                                   | 0.0 (0/11)                    | 0.0 (0/88)                          | 0.3 (1/359)              | >.99                           | >0.99                              |
| Device embolization                                 | 0.0 (0/11)                    | 0.0 (0/88)                          | 0.0 (0/359)              | Undefined                      | Undefined                          |
| Device thrombus                                     | 0.0 (0/11)                    | 2.3 (2/88)                          | 1.9 (7/359)              | >.99                           | .69                                |
| Serious pericardial effusion                        | 0.0 (0/11)                    | 0.0 (0/88)                          | 1.4 (5/359)              | >.99                           | .59                                |
| PE requiring open cardiac surgery                   | 0.0 (0/11)                    | 0.0 (0/88)                          | 0.0 (0/359)              | Undefined                      | Undefined                          |
| PE requiring pericardiocentesis or pericardial puncture | 0.0 (0/11)                    | 0.0 (0/88)                          | 1.1 (4/359)              | >.99                           | >.99                               |
| PE with nonsurgical intervention                    | 0.0 (0/11)                    | 0.0 (0/88)                          | 0.3 (1/359)              | >.99                           | >.99                               |
| Major bleed BARC 3 or 5                             | 0.0 (0/11)                    | 9.1 (8/88)                          | 8.6 (31/359)             | .61                            | .84                                |
| Primary efficacy end point†                         | 100.0 (11/11)                 | 100.0 (80/80)                       | 100.0 (303/303)          | Undefined                      | Undefined                          |
| Complete seal                                       | 90.9 (10/11)                  | 91.3 (73/80)                        | 89.5 (273/305)           | >.99                           | >.99                               |

Values are % (n/total n).

BARC = Bleeding Academic Research Consortium; LAA = left atrial appendage; PE = pulmonary embolism; TIA = transient ischemic attack; WM = Watchman.

*For continuous parameters, $P$ values are based on the Student $t$ test. For categorical parameters, $P$ values are based on the Fisher exact test.

†Rate of effective LAA closure at 12 mo (defined as any peridevice flow with jet size ≤5 mm per core laboratory assessment in implanted patients).
which 38,158 procedures were reported with 7% of cases canceled or aborted. Those who were attempted achieved 98.1% closure with <5 mm peridevice leak, which equates to providing adequate therapy to 91.2% of the intended at-risk population. Major adverse events included pericardial effusion requiring intervention (1.39%) and other major procedural bleeding (1.25%).

We hypothesized that a large proportion of patients enrolled in the single-arm PINNACLE FLX trial were held back specifically by implanting physicians for Watchman FLX on the basis of previously failed attempts at a Watchman 2.5 device or on the basis of prohibitive LAA anatomy for an attempt with Watchman 2.5. We found that a large number (n = 99 [21.6%]) of patients met these criteria and yet the overall safety and effectiveness of LAAC in PINNACLE FLX, including roll-in cases, remained high.

Our study cohort included 11 subjects who had a prior failed attempt at Watchman 2.5 and all 11 were successfully implanted with a Watchman FLX device, with no embolizations or pericardial effusions, and 10 of 11 had zero detectable peridevice leak at 45 days and 12-month postimplant TEE. This observation alone supports a significant improvement in the safety and capability of Watchman FLX as many of the study cohort cases included anterior chicken wing LAA anatomy, previously shown to be an independent risk of pericardial effusion and failure to implant successfully. The Watchman postapproval study data reported a 0.24% device embolization rate, with 6 cases requiring surgical removal in a cohort of 3653 implanted devices. Given 21.6% of the PINNACLE FLX enrollees had anatomic challenges that prevented a successful LAAC with Watchman 2.5, no embolization or effusion requiring surgery supports improved safety of the Watchman FLX device. The majority of subjects in the prohibitive anatomy cohort (mean LAA diameter 18 mm) were not implanted with a 35 mm FLX device for large LAA ostia >31 mm, but rather were subjects with challenging LAA morphology, restrictive LAA depth, or ostia <17 mm.

Our analysis revealed several expected observations and 1 major finding that requires further study. Patients in the prohibitive cohort had procedural factors indicative of a more challenging implant; contrast use, fluoroscopy time, total procedure time, and use of the 20 mm Watchman FLX was significantly higher in the cohort of patients with anatomy restrictions. Many of these subjects had LAA dimensions <17 mm and were typically closed using the 20 mm device; (in prohibitive anatomy cohort 20 mm FLX device was implanted in 37.6% (32 of 85) vs 4.2% (15 of 356) in controls.

![Kaplan-Meier Survival Rates: All-Cause Death](image)

**Figure 3** Kaplan-Meier overall survival curve for PINNACLE FLX failed Watchman (WM) 2.5 cohort (red), prohibitive anatomy cohort (blue), and control cohort (black).
The LAA ostium width >31.5 mm remained an exclusion for use of the 35 mm FLX device (similar for Watchman 2.5), and notably the frequency of use of the 35 mm device was higher in patients with a previously failed attempt at Watchman 2.5 (3 of 11 [27.3%] vs 26 of 356 [7.3%] in controls; \( P = 0.047 \)). Device implant and procedural data indicated cases after a prior failed attempt at Watchman 2.5 or prohibitive anatomy to be more challenging, require more recaptures, sheath exchanges, and devices at the margins of sizing (20 or 35 mm). Despite this, implant success remained high with excellent safety.

The observation that the prohibitive anatomy cohort had both significantly lower overall (1.2% vs 8.8%) and cardiovascular (0% vs 4.7%) mortality than did the control group was unexpected (\( P = 0.02 \)). This was not explained by a difference in age, sex, CHA2DS2-VASc score, HAS-BLED score, device-related thrombus rate, or procedural safety or efficacy. The prohibitive cohort patients were less likely to have systolic heart failure (LVEF slightly higher: 58.0% ± 8.5% vs 55.7% ± 8.4%; \( P = 0.02 \)). Additionally, they had significantly smaller LAA ostia diameter and depth (18.0 ± 4 mm vs 20.4 ± 3 mm; \( P = 0.001 \) and length 23.7 ± 5 mm vs 28.9 ± 5 mm; \( P = 0.001 \)). Although a small difference in LVEF could manifest in a lower event rate related to heart failure hospitalization, or possibly the increased mortality effect could relate to downstream complications from late pericardial effusions in controls (n = 5 control cohort; n = 0 study cohorts), the results indicate a strong protective effect associated with smaller LAA dimensions. Whether LAA size or depth itself could serve as a marker for predicting cardiovascular mortality risk in the absence of a Watchman FLX device warrants careful analysis.

Limitations
PINNACLE FLX was a single-arm trial, and this study is a post hoc analysis, not prespecified or powered to detect a difference between cohorts. Mortality findings are hypothesis generating only. The proportion of Watchman 2.5–ineligible patients may not be representative of the general population because some centers may have preferentially enrolled prior failures. The method of determining “ineligibility” was based on LAA dimensions or anatomy on TEE as assessed by the core laboratory; the study did not initially record other aspects of unsuitable anatomy, such as specific LAA morphology description. Nonetheless, the results suggest that the Watchman FLX device can safely and successfully treat a much broader range of patients than the
earlier-generation Watchman 2.5 device. These results should be confirmed with further research.

**Conclusion**

Despite many PINNACLE FLX enrollees having a prior failed Watchman 2.5 attempt or prohibitive LAA anatomy, implant success with Watchman FLX remained high with no major adverse events.

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**References**

1. Marzec L, Wang J, Shah N, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. J Am Coll Cardiol 2017;69:2475–2484.
2. Yaghi S, Song C, Gray W, et al. Left atrial appendage function and stroke risk. Stroke 2015;46:3554–3559.
3. Holmes D, Alkhouli M, Reddy V. Left atrial appendage occlusion for the unmet clinical needs of stroke prevention in nonvalvular atrial fibrillation. Mayo Clin Proc 2019;94:864–874.
4. Reddy V, Gibson D, Kar S, et al. Post-approval U.S. experience with left atrialappendage closure for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2017;69:253–261.
5. Holmes D, Reddy V, Turi Z, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. Lancet 2009;374:534–542.
6. Holmes DJ, Kar S, Price M, et al. 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 2014;64:1–12.
7. Reddy VY, Holmes D, Doshi SK, et al. The safety of percutaneous left atrial appendage closure: results from PROTECT AF and the Continued Access Registry. Circulation 2011;123:417–424.
8. Reddy VY, Doshi SK, Sievert H, et al. 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 2013;127:720–729.
9. Boersma LV, Ince H, Köche S, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-year follow-up outcome data of the EWOLUTION trial. Heart Rhythm 2017;14:1302–1308.
10. Ellis CR, Metawee M, Piana RN, et al. Feasibility of left atrial appendage device closure following chronically failed surgical ligation. Heart Rhythm 2019;16:12–17.
11. Venkataraman G, Strickberger SA, Doshi S, et al. Short-term safety and efficacy of left atrial appendage closure with the WATCHMAN device in patients with small left atrial appendage ostia. J Cardiovasc Electrophysiol 2018;29:17–21.
12. Murkara S, Lazkani M, Moualla S, et al. Left atrial anatomy and patient-related factors associated with adverse outcomes with the Watchman device—a real world experience. J Interv Cardiol 2017;30:163–169.
13. Freeman JV, Varosy P, Price MJ, et al. The NCDR Left Atrial Appendage Occlusion Registry. J Am Coll Cardiol 2020;75:1503–1518.