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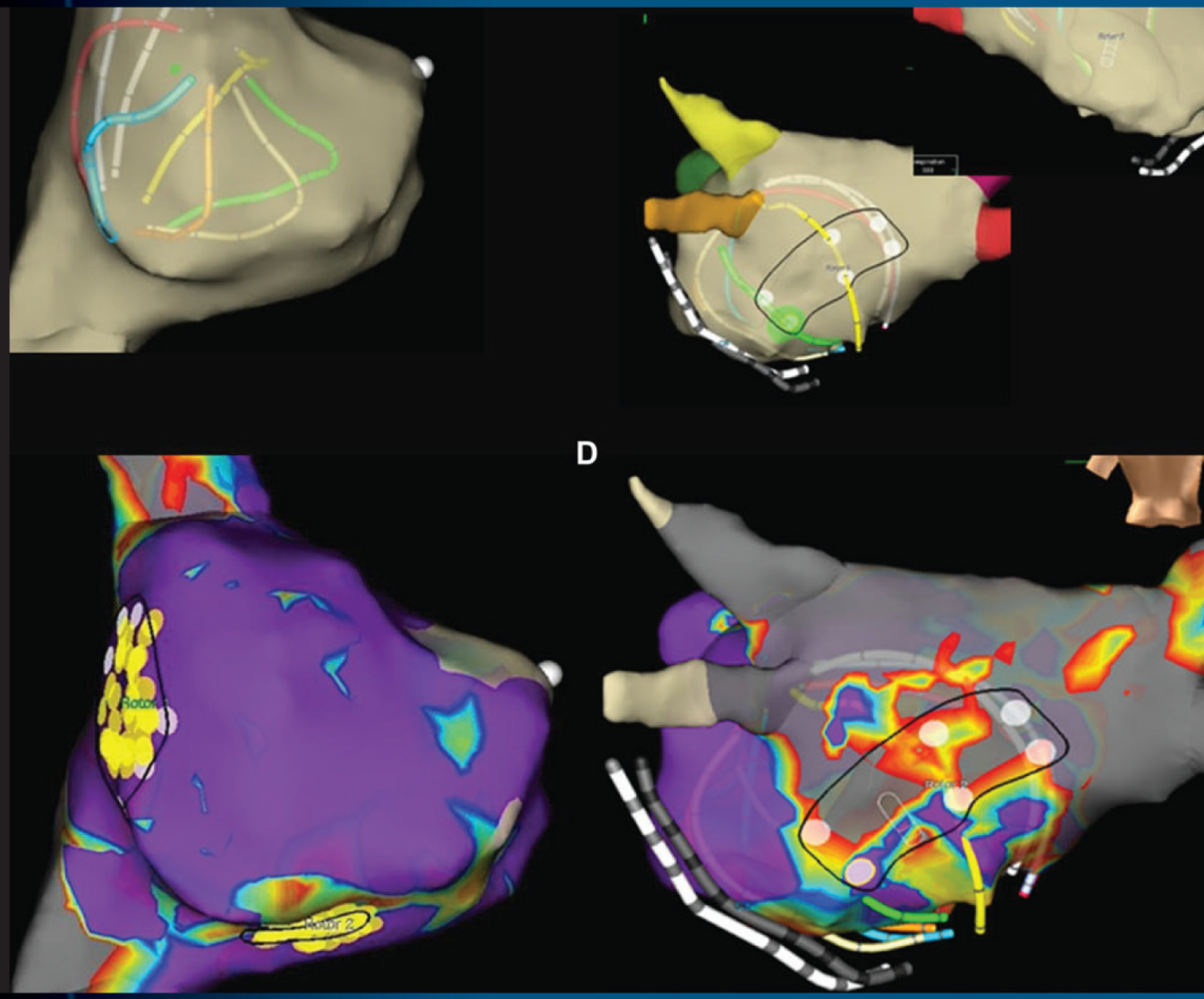

WILEY

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ORIGINAL ARTICLE

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Safety profiles of percutaneous left atrial appendage closure devices: An analysis of the Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) database from 2009 to 2016

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Abstract

Background: Percutaneous left atrial appendage closure (LAAC) is a viable option for AF patients who are unable to tolerate long-term oral anticoagulation (OAC).

Objective: We sought to assess the safety of two commonly used percutaneous devices for LAA closure in the United States by analysis of surveillance data from the FDA Manufacturer and User Facility Device Experience (MAUDE) database.

Methods: The MAUDE database was queried between May 1, 2006 and May 1, 2016 for LARIAT® (SentreHEART Inc., Redwood City, CA, USA) and WATCHMAN™ (Boston Scientific Corp., Marlborough, MA, USA) devices. Among 622 retrieved medical device reports, 356 unique and relevant reports were analyzed. The cumulative incidence of safety events was calculated over the study period and compared between the two devices.

Results: LAAC was performed with LARIAT in 4,889 cases. WATCHMAN was implanted in 2,027 patients prior to FDA approval in March 2015 and 3,822 patients postapproval. The composite outcome of stroke/TIA, pericardiocentesis, cardiac surgery, and death occurred more frequently with WATCHMAN (cumulative incidence, 1.93% vs. 1.15%; P = 0.001). The same phenomenon was observed when comparing the WATCHMAN pre- and postapproval experiences for the composite outcome, as well as device embolization, cardiac surgery, and myocardial infarction.

Conclusions: MAUDE-reported data show that postapproval, new technology adoption is fraught with increased complications. Improved collaboration between operators, device manufacturers, and regulators can better serve patients through increased transparency and practical postmarket training and monitoring mechanisms.

KEYWORDS

air embolism, atrial fibrillation, cardiac surgery, Food and Drug Administration, LARIAT, left atrial appendage closure, left atrial appendage occlusion, malfunction, mortality, outcomes, pericardial effusion, stroke, transient ischemic attack, WATCHMAN

1 | INTRODUCTION

Atrial fibrillation (AF) affects an estimated 2.3 to 5.1 million Americans by contemporary estimates and is known as a leading cause of stroke.[1–3] The left atrial appendage (LAA) is thought to be the major nidus for systemic thromboembolism in AF. Oral anticoagulation (OAC) based on the $CHADS_2$ or CHA_2DS_2-VASc scores has traditionally been the mainstay of stroke prevention in AF,[4] but it has been limited to a degree by factors including risk of bleeding, the need for ongoing monitoring within a relatively narrow therapeutic window, and patient adherence.[5–8] Several new strategies for percutaneous left atrial appendage closure (LAAC) have emerged for AF patients with elevated stroke risk and contraindication or intolerance to long-term OAC.[9,10] Two are currently approved by the Food and Drug Administration (FDA) for use in the United States: the WATCHMAN™ device (Boston Scientific Corp., Marlborough, MA, USA), which is approved for use in stroke prevention in appropriate candidates, and the LARIAT® Suture Delivery Device (SentreHEART, Inc., Redwood City, CA, USA), which has FDA 510(k) approval for soft tissue ligation and is used in an "off label" fashion for LAAC in patients with contraindications to OAC. The objective of this study was to evaluate and compare the safety profiles of these two devices, as assessed by FDA MAUDE medical device reports (MDRs) of events associated with each device.

2 | METHODS

The MAUDE database was queried on May 1, 2016 for MDRs pertaining to the WATCHMAN and LARIAT devices.

2.1 | FDA MAUDE Database

The MAUDE database is an electronic repository of adverse events involving medical devices. Its data include voluntary reports, as well as reports from user facilities (e.g., hospitals, outpatient facilities, nursing homes, and ambulatory surgical centers), distributors, and manufacturers since the early 1990s. The database is updated monthly and can be accessed electronically at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM.

Of particular importance, MAUDE reporters are classified into two groups: (1) mandatory reporters (manufacturers, importers, and device user facilities) and (2) voluntary reporters (healthcare professionals, patients, and consumers).

2.2 | Search strategy

A MAUDE database search was conducted for reports received from May 1, 2006 to May 1, 2016 to capture all MDRs pertaining to the two devices. To optimize the sensitivity of the search strategy, the initial search was conducted with the product names "WATCHMAN" and "LARIAT" alone in the "brand name" field of the "advanced search." This yielded 455 results for the WATCHMAN device, including both MDRs pertaining to the "WATCHMAN Access System" and the "WATCHMAN LAA Closure Device & Delivery System." A preliminary search for "LARIAT" alone returned 72 results. Because the individual components comprising the LARIAT device, including the "EndoCATH® Large Occlusion Balloon," "FindrWIRZ® Guide Wire System," "SofTIP™ Guide Cannula," "TenSURE™ Suture Tightener for LARIAT," and "SureCUT™ Suture Cutter," are also either trademarked or registered, these were searched individually in the "brand name" field. In addition, a separate search was conducted for "SentreHEART" in the "manufacturer" field by itself to attempt to capture any LARIAT-related reports filed either under the implicated component of the system, or the manufacturer alone.

2.3 | MDR screening

An overview of the search and screening strategy used to identify MDRs for analysis is shown in Figure 1. In total, 167 MDRs were identified pertaining to the LARIAT device, along with 455 MDRs for WATCHMAN, for a combined total of 622 MDRs. These were reviewed and screened for duplicates given the possibility of multiple reporters, as well as multiple individually trademarked components in the case of LARIAT. A total of 194 redundant entries were identified (126 for WATCHMAN and 68 for LARIAT). In addition, 47 of the initial 167 LARIAT reports were irrelevant to the actual suture delivery device, while 25 WATCHMAN reports, including 12 deaths, contained inadequate data to be included for analysis. These are further detailed in the Supplement (see Supplement 1.1, 1.2). Following screening, a total of 356 MDRs were included for analysis.

2.4 | Statistical analysis

Events were adjudicated and tallied based on review of the event description for each MDR. Periprocedural events were tallied where documented. Malfunctions were broadly defined as event reports in which there was documentation of inability to successfully carry out the procedure due to technical limitation and were further divided to indicate the implicated component of the respective device, based on the narrative from the MDR. Deaths were included from reports documenting their occurrence in the periprocedural period or related to a cardiovascular cause at later points in time. Pericardial effusions were documented in cases where an effusion or its treatment was explicitly described. If the patient was managed with pericardiocentesis and ultimately converted to surgery, both procedures were tallied. On the other hand, if the patient underwent cardiac surgery it was not assumed that they also received pericardiocentesis.

The cumulative incidence of individual events was computed using, for LARIAT, the manufacturer's report of total cases performed over the duration of the study (Personal Communication, SentreHEART, Inc., August 19, 2016). The same was done for WATCHMAN using the total number of cases performed in the trial (PROTECT AF, PREVAIL) and registry (CAP1, CAP2) populations prior to market approval, as well as the published post-marketing experience.[11,12] These periods coincided with the period of our MAUDE query (i.e., from initial use of both devices until May 2016). Cumulative incidences of complications were compared between devices over the duration of the study period using the chi-squared test. Incidence proportion was also compared in

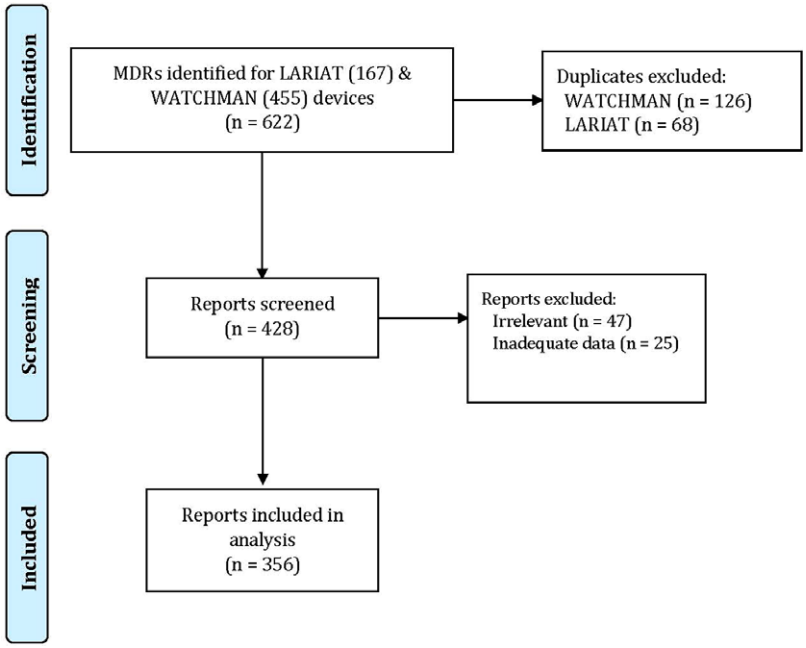

FIGURE 1 FDA MAUDE database search strategy and screening of medical device reports (MDRs) [Color figure can be viewed at wileyonlinelibrary.com]

the pre- and postapproval populations with WATCHMAN as the number of cases performed in each period was known.

3 | RESULTS

3.1 | LARIAT safety profile

Results of the MAUDE database analysis for MDRs pertaining to the LARIAT device included 136 events reported in 52 MDRs, accounting for multiple events described in the same report. These are represented visually in Figure 2 and in tabular form in the Supplement (Section 2.1, Table 1). The manufacturer reported the number of LARIAT cases performed in this period to be 4,889, yielding a cumulative event incidence of 2.7%. The most frequent complications reported were: pericardial effusions in 46 (0.94%), need for cardiac surgery in 38 (0.78%), and pericardiocentesis in 23 (0.47%).

3.2 | Pericardial effusion, blood transfusion, and urgent cardiac surgery

Among the reports of pericardial effusion, 42 of 46 (91.3%) were attributed to LAA perforation, while the remaining four reports were felt to be secondary to right ventricular perforation. In eight cases

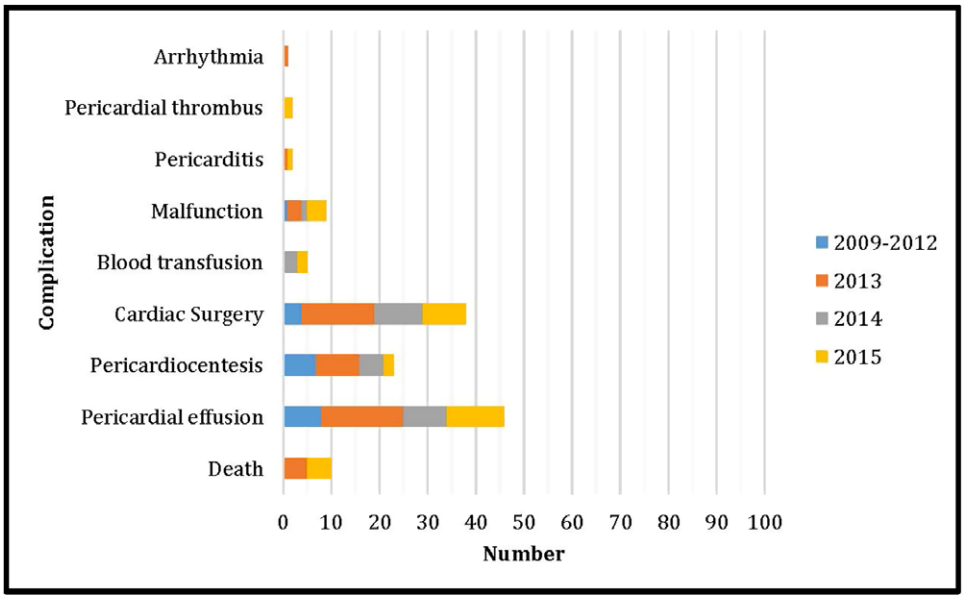

FIGURE 2 LARIAT device complications reported in FDA MAUDE database (2009–2016) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Cumulative incidence of events/complications occurring in LARIAT and WATCHMAN devices over the course of the study period (2009–2016) and further comparison of pre- and post-FDA approval periods with the WATCHMAN device

	LARIAT	WATCHMAN	LARIAT vs. WATCHMAN (P Value)	WATCHMAN Preapproval	WATCHMAN Postapproval	Pre- vs. Postapproval WATCHMAN (P Value)
Composite (death, CVA/TIA, pericardiocentesis, cardiac surgery)	1.15%	1.93%	**0.001**	0.69%	2.12%	**<0.0001**
Death	0.21%	0.34%	0.18	0.25%	0.39%	0.3659
Stroke/TIA	0.00%	0.32%		0.25%	0.34%	0.5412
Pericardiocentesis	0.47%	0.98%	**0.002**	0.20%	1.39%	**<0.0001**
Cardiac surgery	0.78%	0.63%	0.37	0.05%	0.94%	**<0.0001**
Device embolization		0.46%		0.05%	0.68%	**0.0007**
Cardiac thrombus		0.79%		0.54%	0.92%	0.1244
Need for transfusion	0.10%	0.39%	**0.003**	0.20%	0.50%	0.081
Malfunction	0.18%	1.66%	**<0.001**	0.10%	2.49%	**<0.0001**
Air embolism		0.15%		0.05%	0.21%	0.137
Cardiac ischemia		0.15%		0.00%	0.24%	**0.029**
Groin complication		0.31%		0.25%	0.34%	0.5412

(17.4%), pericardiocentesis alone was performed for management without conversion to surgery, while in 23 of 46 cases (50%), patients received surgical intervention without documented pericardiocentesis. In five reports (10.9%), the need for blood product transfusion was noted; all five cases involved surgical intervention. There were two (0.04%) cases of pericardial thrombus, both treated with surgical evacuation, as well as two cases of pericarditis.

3.3 | Strokes, transient ischemic attacks, device-related leaks, and thrombi

No peri-procedural or long-term, postprocedure strokes or transient ischemic attacks (TIAs) were reported in the MAUDE database in association with LARIAT. Similarly, no reports on associated device-related leaks or thrombi were identified. Furthermore, there were no complications reported in the MAUDE database for the LARIAT system in the portion of 2016 included in the study period, at the time of the query.

3.4 | Mortality

A total of 10 (0.20%) deaths were reported in association with LARIAT. Five were reported in 2013 and five in 2015; these are described in further detail in the Supplement (Section 2.3, Table 2). Among the deaths, six of 10 involved tightening of the suture around the LAA. In two cases, the entire knot came free of the LAA, while in another case only a portion of the LAA had been captured by the LARIAT, it later became known. In two other cases, tightening of the suture was closely followed by development of an effusion. In one case, the patient's family declined surgical intervention or resuscitation. In the remaining cases, resistance was noted on attempting to remove the device, and further manipulation resulted in hemodynamic compromise.

TABLE 2 Comparison of reported WATCHMAN postapproval periprocedural complications based on our analysis of MAUDE and that reported by Reddy et al. using Boston Scientific Corp. clinical specialist documentation. Reported as number of events (percentage). Percentage reflects cumulative incidence from March 2015 to May 2016

Complications	Reddy et al. Experience[11]	MAUDE-Reported Events
Pericardial tamponade	39 (1.02)	58 (1.52)
➢ Treated with pericardiocentesis	24 (0.63)	33 (0.86)
➢ Treated surgically	12 (0.31)	25 (0.65)
➢ Resulted in death	3 (0.078)	10 (0.26)
Pericardial effusion, no intervention	11 (0.29)	17 (0.44)
Procedure-related stroke	3 (0.078)	6 (0.16)
Device embolization	9 (0.24)	20 (0.52)
➢ Removed percutaneously	3 (0.078)	10 (0.26)
➢ Removed surgically	6 (0.16)	10 (0.26)
Death	4 (0.10)	12 (0.31)
➢ Procedure-related mortality	3 (0.078)	6 (0.16)
➢ Additional mortality within 7 days	1 (0.026)	6 (0.16)

3.5 | WATCHMAN safety profile

A total of 472 events (cumulative incidence, 8.1%) were reported in 304 MDRs for WATCHMAN, which reflect a reported 5,849 WATCHMAN cases performed over the study period. The key reported events are shown in Figure 3. The most frequently reported among these included: device malfunction in 97 (1.7%), pericardial effusion in 84 (1.4%), a need for pericardiocentesis in 57 (0.97%), and intracardiac

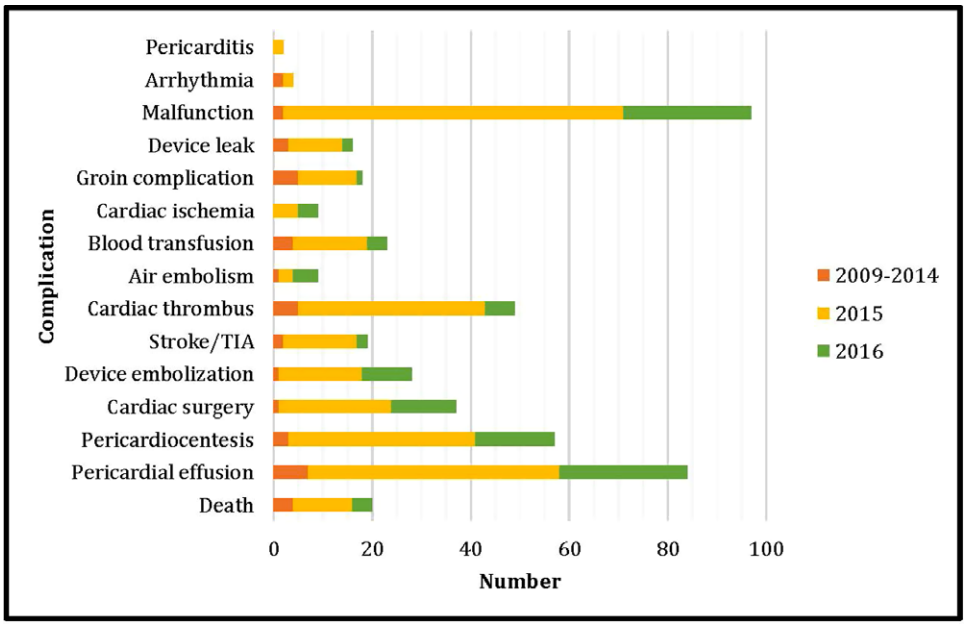

FIGURE 3 WATCHMAN device complications reported in FDA MAUDE database (2009–2016) [Color figure can be viewed at wileyonlinelibrary.com]

thrombus in 49 (0.84%). Reported events/complications for WATCHMAN are described in further detail in the Supplement (Section 3–3.1 to 3.9) and in Table S3.

3.6 | Pericardial effusion, pericardiocentesis, and urgent cardiac surgery

Pericardial effusions were described in 84 (1.4%) WATCHMAN MDRs. Among these, 20 of 84 (23.8%) were managed conservatively, while in 57 cases (67.9%) patients underwent pericardiocentesis. Twenty (35.1%) of 57 patients were subsequently converted to surgery after pericardiocentesis. Another six of 84 (7.1%) were taken directly to surgery without reported pericardiocentesis, for a total of 31% of cases with pericardial effusions ultimately requiring surgical intervention. Aside from the 26 cardiac surgeries for hemodynamically significant effusions, 11 others were performed to manage device embolizations. Embolizations occurred in 27 (0.46%) cases, and their individual management is discussed in further detail in the Supplement (Section 3.4).

3.7 | Stroke and TIA

Either stroke or TIA was noted in 19 (0.33%) WATCHMAN reports with 15 of 19 reported as strokes and the remainder classified as TIAs. An approximation of time elapsed since WATCHMAN implantation was available in 15 of 19 (79%). Among these, three cases occurred in the immediate postimplantation period (within the first 2 hours, postprocedure). Additional events up to 6 weeks and between 6 weeks and 1 year postimplantation were reported in three and three cases, respectively. The remaining six cases occurred between 1 and 5 years postimplantation with half occurring beyond 3 years. Device-related thrombi were detected in two of 19 (10.5%) cases, while another three of 19 (15.8%) noted incomplete LAA closure, and, finally two of 19 were attributed to cerebral air emboli (AE).

3.8 | AE and cardiac thrombi

AE were noted to occur in 9 (0.15%) WATCHMAN patients. Two were cerebral AE, while four of nine AE were implicated in periprocedural myocardial ischemia marked by ST-segment elevation and hypotension. In 49 (0.84%) WATCHMAN reports, intracardiac thrombus was described with eight of 49 (16.3%) noted intra-procedurally and the remainder observed postprocedure. Among the latter, 37 were device-related thrombi, with seven of them noted between 1 and 10 years postimplantation. Thrombi were found in cases of peri-device leak, stroke, and death in three, two, and three cases, respectively, and are discussed further along with their management in the Supplement (Sections 3.3, 3.5).

3.9 | Mortality

Twenty deaths (0.34% of WATCHMAN events) reported in the MAUDE database were analyzed for the WATCHMAN device, following exclusion of 12 reports of death as outlined in Methods and in the Supplement (3.9, Table S4). Thirteen of 20 (65%) had a clear cardiovascular cause described in the MDR. Six of these of these involved a cardiac arrest, three in the setting of LAA perforation, two in the setting of postprocedural infection, and one likely related to device embolization (found in mitral valve apparatus).

3.10 | Comparison of reported events for LARIAT and WATCHMAN

A comparison of the cumulative incidence of key reported events for each device is shown in Table 1, along with a comparison of the pre- and post-FDA approval events for the WATCHMAN device. The composite of major complications, including stroke/TIA, need for pericardiocentesis, need for cardiac surgery (in the absence of pericardiocentesis),

and death, occurred less frequently with LARIAT as compared to WATCHMAN (1.15% vs. 1.93%; P = 0.001), driven primarily by differences in stroke/TIA events and need for pericardiocentesis. There was no significant difference in mortality between the two devices over the study period. Comparing the pre- and postapproval experiences with WATCHMAN, a significant increase in event rates, including the composite endpoint, need for cardiac surgery, device embolization, device malfunction, and cardiac ischemia was noted in the postapproval period. There were no significant differences in the rate of death, stroke/TIA, cardiac thrombus, need for transfusion, AE, or groin complications.

4 | DISCUSSION

In the present study, we found that for two commonly used LAAC modalities, the LARIAT and WATCHMAN devices, following adoption into clinical practice there were quite a few reported safety events documented in the FDA MAUDE database. This was true despite the different approval mechanisms for the two devices, with the LARIAT receiving 510(k) approval for soft tissue ligation with off-label use for LAAC, while WATCHMAN was approved through the FDA premarket approval (PMA) pathway, which entailed two randomized controlled trials, two prospective registries, and multiple rounds of FDA Circulatory Systems Advisory Panel review prior to approval. Second, we found that over the period from 2009 to 2016, the cumulative incidence of a composite measure of stroke/TIA, need for pericardiocentesis or cardiac surgery, and death was greater for the WATCHMAN device as compared to the LARIAT. Furthermore, these and other events occurred more frequently in the WATCHMAN postapproval period as compared to the period before FDA approval. One possible explanation for this phenomenon is that following FDA approval of the WATCHMAN device, the group of operators able to implant the device rapidly expanded from experienced study investigators to include numerous, less experienced operators, potentially leading to the observed increase in complications for a procedure with an admittedly steep learning curve. On the other hand, with its alternative approval pathway and more limited roll-out, the LARIAT experience was primarily driven by a smaller group of operators who believed in its potential and off-label use, while gaining incremental experience with the device over time, perhaps limiting complications related to operator inexperience.

4.1 | Device development

The WATCHMAN received conditional approval through the PMA pathway in 2010 based on the findings of the PROTECT AF trial,[13] which demonstrated its non-inferiority versus warfarin in the combined efficacy endpoint of all-cause stroke, systemic thromboembolism, and cardiovascular/unexplained death. Additional postapproval study was required due to safety concerns stemming from a reported 9% procedure failure rate, 4.8% rate of pericardial effusions prompting urgent intervention, and a 1.1% rate of periprocedural stroke.[13] This led to completion of the PREVAIL randomized controlled trial,[14] as well as creation of two related registries.[12,15] The cumulative data generated from these studies were reviewed in an unprecedented third FDA Circulatory Systems Advisory Panel meeting, at which time it was determined based on the totality of the data that the WATCHMAN device was safe, though concerns about its efficacy compared to warfarin persisted, due to a series of late ischemic strokes in the device group, which collectively rendered the WATCHMAN unable to meet its second coprimary efficacy endpoint in PREVAIL.[16]

The LARIAT device was granted FDA 510(k) approval for use in soft tissue approximation in 2006.[17] In the context of LAAC, LARIAT is used "off label" in the United States. It is thought to be of particular benefit in AF patients with high stroke risk in whom systemic anticoagulation is contraindicated and has also shown promise in reducing AF burden through electrical isolation of the LAA, as well as favorable neurohormonal effects.[18,19] Like the WATCHMAN, it carries Conformité Européenne (CE) approval for marketing in Europe. Multiple small, observational studies have supported its efficacy and safety for LAA closure,[20–22] but a recent systematic review including a MAUDE database query identified five deaths and 23 urgent cardiac surgeries following LARIAT procedures, raising concerns about its Class II designation and prompting an FDA safety communication.[23,24] Currently, the LARIAT device is the subject of the aMAZE (LAA Ligation Adjunctive to PVI for Persistent or Longstanding Persistent Atrial Fibrillation) randomized controlled trial (ClinicalTrials.gov Identifier: NCT02513797).[25]

4.2 | Temporal trends in device safety and comparison with study-reported complications

One of the barriers to interpreting data from the MAUDE database is the absence of a clearly defined number of patients receiving either therapy over time, precluding calculation of a precise incidence for any event/complication. With respect to the LARIAT device, it is known from the device manufacturer that in the United States, 4,889 cases were completed over the duration of the study period. The number of cases performed per month remained relatively constant during that time with a 10–20% reduction in the years 2015–2016 due to a combination of factors, including an FDA safety communication, approval of the WATCHMAN in the United States in March 2015, and initiation of a major clinical trial for LARIAT. The overall trend, as demonstrated in Figure 4, is one of increasing complications peaking in 2013 with subsequent decline, though this is likely less dramatic when accounting for the reduction in number of performed cases. During this span, refinements for the LARIAT included improved patient selection with increased operator experience, the adoption of a micropuncture needle and telescoping technique for "dry" pericardial access, and periprocedural colchicine for pericarditis prophylaxis.[21,26,27] Despite the overall favorable trend, LARIAT-related MAUDE data suffer from underreporting, as evidenced by the absence of reports for postprocedural LAA leaks and intracardiac thrombi, which are well-documented in the literature.[28–30]

The number of WATCHMAN procedures performed during the same period was 5,849.[11] The cumulative incidence of MAUDE-reported events was 8.1% during that time. Furthermore, as

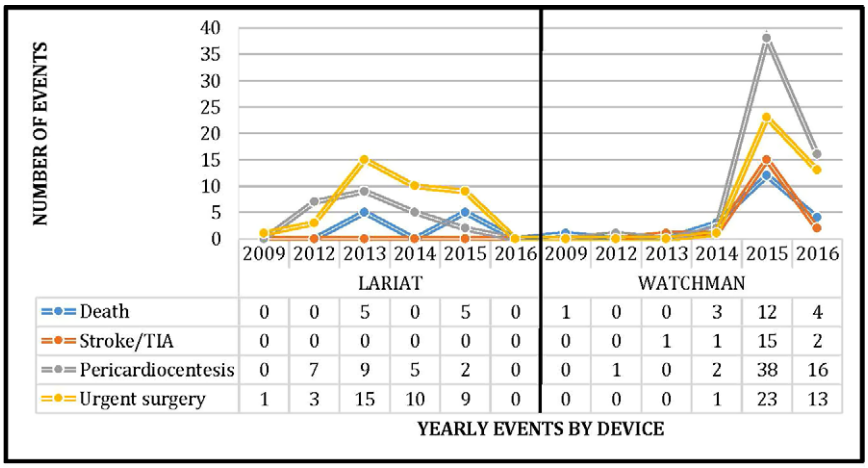

FIGURE 4 Temporal trends in complications reported by absolute number as documented in the FDA MAUDE database for WATCHMAN and LARIAT devices (2009–2016) [Color figure can be viewed at wileyonlinelibrary.com]

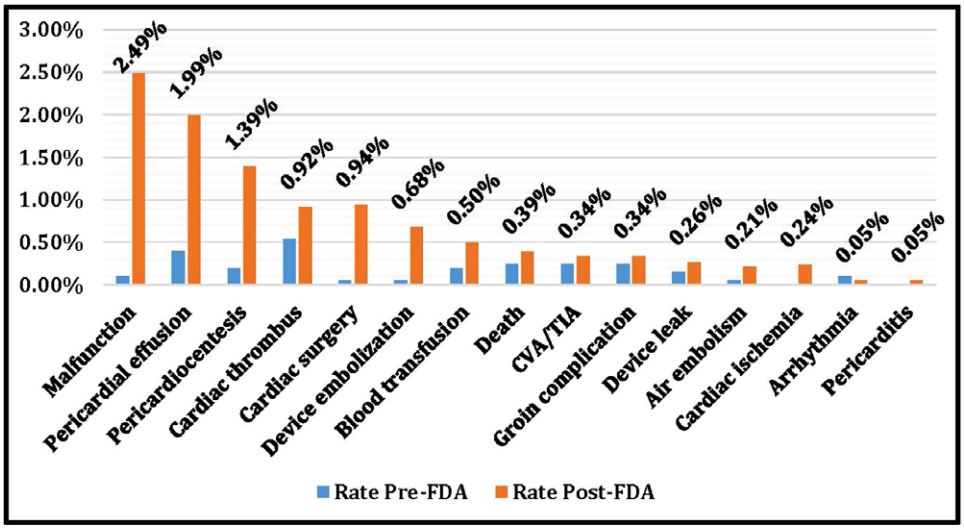

FIGURE 5 Comparison of FDA MAUDE-reported events for WATCHMAN prior to (Pre-FDA) and following (Post-FDA) approval from the FDA (March 13, 2015). Percentages shown refer to postapproval cumulative incidence [Color figure can be viewed at wileyonlinelibrary.com]

illustrated in Figure 5, a substantial increase can be appreciated in most reported events/complications. This is particularly telling given the strict reporting requirements during the WATCHMAN clinical trials, whereas the postapproval reports were more prone to underreporting in the MAUDE system of passive surveillance. Also notable is the fact that six reported events occurring in 2015 could not be included due to lack of a clear event date to distinguish whether they were pre- or postapproval events. Similar to LARIAT, MAUDE-reported data for WATCHMAN are also weakened by underreporting. Simply considering the publicly available data presented to the FDA in October 2014, a total of 54 cardiovascular/unexplained deaths and 173 all-cause deaths were detailed, both of which dwarf data available in MAUDE even as our query extended an additional 7 months beyond the date of the FDA presentation.[31]

Furthermore, it is concerning to observe that in a recent publication of the post-FDA approval WATCHMAN experience,[11] which assessed device safety and efficacy based on de-identified reports completed by manufacturer representatives attending each case, documented safety events were far less in number as compared to the findings of our study (Table 2). This may in part be related to technical differences in the adjudication process or the fact that the source reports from that study purportedly reflected periprocedural outcomes over a 7-day period, whereas MAUDE reports may have been filed at later times to describe periprocedural safety events.

5 | STUDY LIMITATIONS

Unfortunately, the MAUDE database provides only a superficial view of a device's safety profile. Whereas the FDA has tremendous authority vis-à-vis device manufacturers and user facilities, the same is not true of its relationship with healthcare professionals, regarded as voluntary reporters, which lends itself to a conflicted relationship between industry and providers.[32–34] Notable limitations of the database itself include:

1. Significant heterogeneity in reporting/lack of binding commitment to report by many key stakeholders.
2. Clear discrepancies between reported complications/malfunctions and subsequent analysis by the device company (e.g., malfunction reported, manufacturer receives device and states it cannot reproduce the same issue).
3. No accurate correlation between events and outcomes (e.g., device implanted in 2014, patient reportedly died 2015 and no further details are available). In many cases the study/trial name (if applicable), exact date of the event, or other information is redacted.
4. Multiplicity of reports surrounding one event (e.g., patient/family, nurse, physician, device company) with potentially different details.
5. No ongoing assessment of the total number of cases performed per unit time.
6. Potential discrepancies with clinical trial findings and resulting challenges for referring physicians to provide truly informed consent.

Therefore, it is clear that an improved methodology beyond passive surveillance is necessary for timely and accurate detection of important safety signals.

6 | CONCLUSIONS

The temporal trends in post LAA closure device-related adverse events suggest an increase in reported safety events shortly after incorporation into clinical practice. Passive surveillance mechanisms such as the FDA MAUDE database are inadequate for nimble, effective postapproval monitoring. The process stands to be greatly improved with the advent of more rigorous postapproval studies, registry participation, operator training, and the integration of multiple streams of relevant data to improve detection of important safety signals and facilitate a more robust feedback mechanism.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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