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Clinical Data Summary & Discussion
Of the
Ultraseal Left Atrial Appendage (LAA) Closure Device

The clinical data used to support the CE marking of the Ultraseal LAA Closure device comes from three sources.

1. Ultra Close Study
   The report and corresponding protocol for this study is contained in Appendix G of this evaluation.

2. Ultra Close 2 Study
   The report and corresponding protocol for this study is contained in Appendix H of this evaluation.

3. Canadian Special Access implants

   Eighteen patients were implanted with the Ultraseal Left Atrial Appendage Closure device in Canada. These patients were implanted under the provisions Health Canada's Special Access program. The Special Access Program allows the use on unapproved devices within a specific clinical population where no devices are approved for use in Canada. The implant of a device under this program requires three approvals.

   1. Physician approval for each patient.
      The physician determines that the patient is suitable for LAA closure with the device.

   2. Individual Hospital approval for each patient. (local approval)
      The physician must obtain institutional approval for the use of the device. Once obtained the hospital sends a request to Health Canada for a Special Access Permit.

   3. Individual Special Access approval for each patient from Health Canada. (national approval)
      Health Canada reviews the permit request sent by the hospital and makes a decision to grant or deny the permit request. The hospital and the manufacturer of the device are then notified of that decision via facsimile.

   The special access approval by Health Canada indicates that all three of these approvals have been obtained prior to the implant of the device. Health Canada has granted all special access permits for the implant of the Ultraseal LAA Closure

devices. The special access permit approvals for all each device implanted in Canada are included in Appendix I of this evaluation.

Three institutions participated in this program. These institutions and the implanting physicians are as follows.

Institution	**Implanting Physician**
Institut Universitaire De Cardiologie Et De Pneumologie De Québec	Dr. Josep Rodés-Cabau
Montreal Heart Institute	Dr. Reda Ibrahim
Centre hospitalier de l'Université de Montréal	Dr. Jean-Bernard Masson

The data collected on these 18 patients was compiled and analyzed.

Overall Performance Summary & Discussion

The results from each of the clinical data sources listed above are presented in the following table.

Data Source	**Number of Patients**	**Total device Implant Months**	**Device or procedure related Serious of Major Adverse Events**
Ultra Close Study	10	284.57	None
Ultra Close 2 Study	4	66.29	None
Canadian Special Access	18	26	Cardiac Tamponade requiring Drainage
Total	***32***	***376.86***	

The clinical evaluation of the Ultraseal LAA is based on the composite results of these studies and the other supporting animal, biological and bench data presented earlier. The results of these studies demonstrate that the Ultraseal LAA closure device is safe and effective for its intended use, the closure of a LAA in patients with nonvalvular atrial fibrillation.
The implantation of percutaneous LAA occlusion devices highlights certain specific issues unique to the use of this type of device. The following discussion points address some of these issues comparing the results of the Ultraseal LAA Closure device to other approved CE marked percutaneous LAA occlusion devices.

Procedural Issues

One serious or major adverse event occurred during the implant procedure of the Ultraseal LAA Closure device. The event was a cardiac tamponade that required drainage. After drainage the event was completely resolved.

Procedural complications and serious adverse events do occur with other CE marked devices LAA occlusion devices. While many factors not related to the device being implanted may contribute, these events can include stroke, serious pericardial effusion, device embolization with surgical removal and others.

Non-serious adverse events have been reported in small numbers with the use of the Ultraseal LAA Closure device. One small Atrial Septal Defect was reported. In this case the transeptal puncture site had not completed closed at the time point of the follow-up. The physician considered this event as related to the procedure and possible the device but not serious. In addition, one insertion site hematoma was reported. This was also considered non-serious and is a commonly understood complication of catheterization procedures.

Short Term Implant Results (24 hours to 45 days post implant)

No serious or major adverse events have occurred from 24 hours to 45 days post implant. These results add to the overall safety profile of the device. As previously demonstrated with literature for other CE marked devices many issues associated with the implant of an LAA occlusion device can manifest during this time period. For example, the combined results of the PROTECT AF and CAP studies reported the following.

> "*of the 46 and 17 procedural/device related primary safety events observed in the PROTECT AF and CAP studies respectively, approximately 94% (59 of 63) events occurred within 7 days of the implantation.*"

One Ultraseal LAA Closure device embolized in the Ultra Close study between 24 hour and 30 days post follow-up. The device was percutaneously retrieved without further consequences to the patient. This event was determined to be minor based on the definition in the Ultra Close study protocol. This was the only device embolization that has occurred with the implant of the device. This event is consistent with the results reported above for the PROTECT AF and CAP studies.

Thrombus Formations

Thrombus formations on the surface of LAA occlusion devices are not uncommon as previously demonstrated in the literature for CE marked LAA occlusion devices. Thrombus formations on the surface of devices have been reported for the ACP, Amulet and Watchman devices. The rate at which these thrombus formations occur varies widely from publication to publication. Within the articles selected for comparison in the study reports for the Ultraseal LAA occlusion device, the rates of thrombus formations on other devices ranged from 0 to 17.6% from implant to 3 months follow-up. This wide variation may not be specifically device related but may be influenced significantly by the patient's clinical condition such as permanent atrial fibrillation. In the vast majority of cases, patients that have thrombus formations on their implanted devices are successfully treated with anticoagulant medications.

Thrombus formations were also reported with the implant of the Ultra Close LAA Closure device. These patients were successfully treated with anticoagulant medications. This treatment and its results are consistent with those of other CE marked LAA occlusion devices.

One additional thrombus formation was reported in a one case performed in Quebec City, Canada. This thrombus was also successfully resolved with anticoagulant medications.

Closure of the LAA

The purpose of occluding a LAA is to prevent thrombus from being ejected that could lead to embolic stroke. While complete closure of the LAA is the goal of a device implantation the variable nature of the LAA anatomy makes this goal difficult to achieve. The impact of incomplete LAA closure was analyzed by Gonzalez, et al. in the article titled, *The Clinical Impact of Incomplete Left Atrial Appendage Closure with the Watchman Device in Patient with Atrial Fibrillation.* The analysis reported in this study was based on data collected on 485 patients enrolled in the PROTECT AF study. The study reported the following.

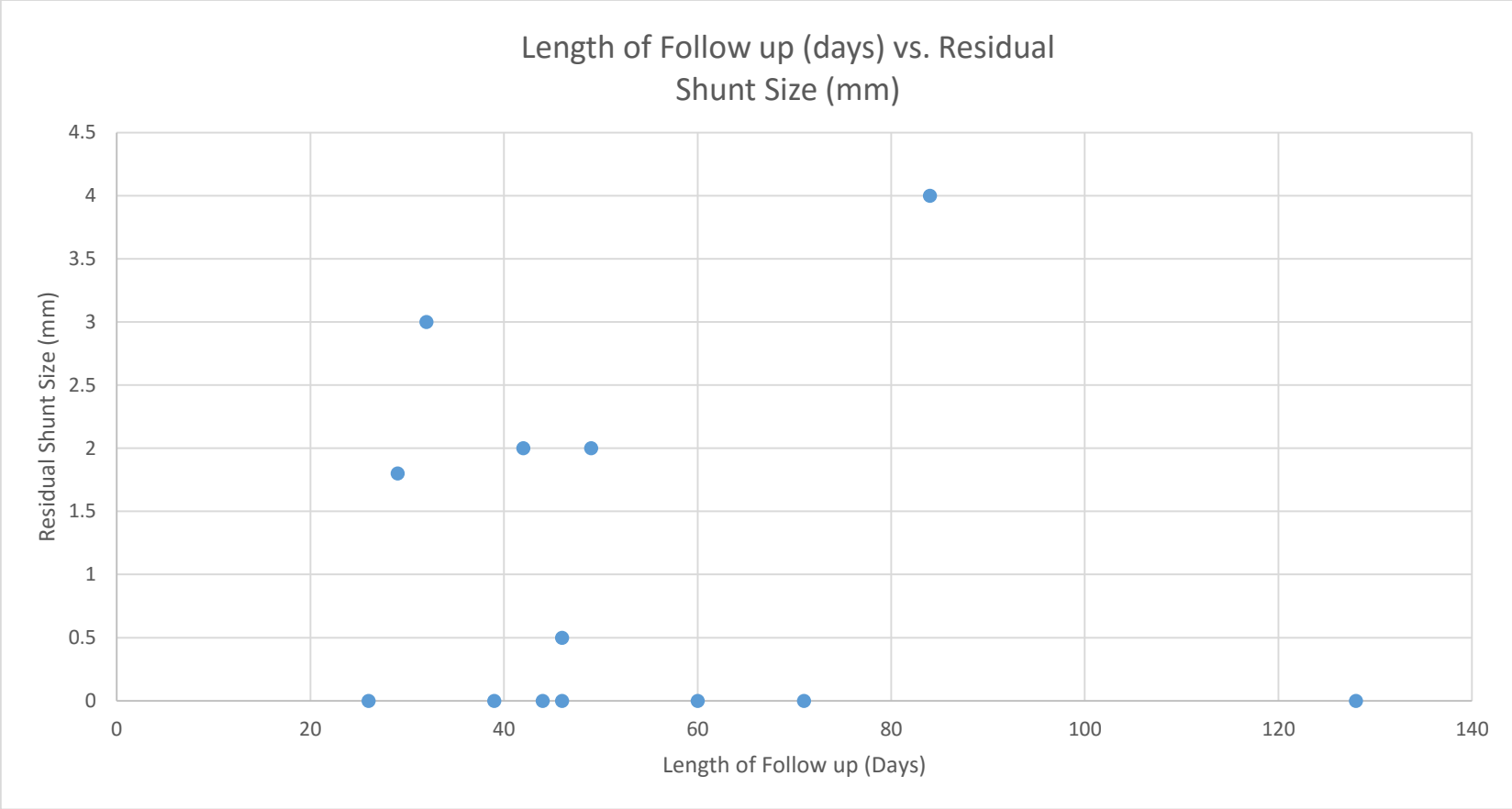
- 40.9% of patients had flow around the device at 45 days post implant
    - Among patients with documented residual flow, the severity of the flow was as follows:
        - Minor (<1mm) in 7.7% of patients
        - Moderate (1-3mm) in 59.9% of patients
        - Major (>3mm) in 32.4% of patients
- 33.8% of patients had flow around the device at 6 months post implant
    - Among patients with documented residual flow, the severity of the flow was as follows:
        - Minor (<1mm) in 2.9% of patients
        - Moderate (1-3mm) in 60% of patients
        - Major (>3mm) in 37.1% of patients
- 32.1% of patients had flow around the device at 12 months post implant
    - Among patients with documented residual flow, the severity of the flow was as follows:
        - Minor (<1mm) in 0.8% of patients
        - Moderate (1-3mm) in 62.4% of patients
        - Major (>3mm) in 36.8% of patients

After performing a statistical analysis on this data, the authors of this article concluded that residual peri-device flow into the LAA after percutaneous closure with the Watchman device was common and is not associated with an increased risk of thromboembolism. This conclusion may be due to the fact that while the LAA is not fully occluded, the presence of the occlusion device is enough to prevent thromboembolism.

The composite closure results of the Ultraseal LAA Closure device across all implants are as follows.

Data Source	30 day Closure Rate	45 day Closure Rate	6 month Closure Rate	Closure definition
Ultra Close Study	71.4%	NA	NA	2mm shunt of less
Ultra Close 2 Study	NA	100%	100%	3mm shunt +/- 2mm

The follow up time points for the Canadian Special Access patients varied. Therefore, the closure rate was measured at multiple time points. The following chart displays those closure rates.



As demonstrated by the chart above, the maximum shunt size measured in the Canadian Special Access patient was 4mm measured at 84 days post implant while many of the implants were completely closed.

The closure rates of the Ultraseal LAA Closure device are similar to those of the WATCHMAN device reported in the study referenced above. This study also demonstrates that small residual shunting in patients that have undergone LAA occlusion may not lead to an increased risk of stroke.

Long Term Implant Results (greater than 45 days post implant)

No serious or major adverse events have occurred after 45 days post implant with the Ultraseal LAA Closure device. As with the reported short term results, this fact adds to the overall safety profile of the device.
As previously demonstrated the combined results of the PROTECT AF and CAP studies reported the following.

> "*of the 46 and 17 procedural/device related primary safety events observed in the PROTECT AF and CAP studies respectively, approximately 94% (59 of 63) events occurred within 7 days of the implantation.*"

This means that only 6% of events occurred after 7 days of implantation. Complications from the procedure and implant of the WATCHMAN device are much more prevalent prior to 45 days of implant. This is likely due to the reported procedural complications such as procedural stroke and pericardial effusion also reported with the ACP and Amulet device. This clearly places an emphasis on short term safety for LAA occlusion devices. While long term results are clearly important, this data demonstrates that this time period is less likely to produce serious adverse events.

The physicians that implanted devices in the Ultra Close and Ultra Close 2 studies confirmed in September 2015 that no additional adverse events had occurred in any of the patients enrolled in these studies since the last reported follow-up. For patients enrolled in the Ultra Close study this represented between 21 and 25 months of adverse event reporting. For patients involved in the Ultra Close 2 study this represents approximately 15 months of adverse event reporting. Information beyond 30 day data has not been reported for the Canadian Special Access patients. This information confirms the positive long term implant results with the Ultra Close LAA Closure device.

Additional Implants

An additional 15 patients have been implanted with the Ultraseal LAA Closure device since the CE mark submission. No adverse events occurred during the implant or follow-up of these patients to date.