Percutaneous Left Atrial Appendage Occlusion for Stroke Prevention in Patients with Atrial Fibrillation

Cumulative Procedural Experience with the AMPLATZER Cardiac Plug
Abstract

Oral anticoagulation (OAC) is a highly effective therapy to prevent stroke in patients with atrial fibrillation (AF). However, OAC therapy is associated with the risk of bleeding, may be complicated to manage and impeded by patient's incompliance. Percutaneous occlusion of the left atrial appendage (LAA) has emerged as a possible alternative to overcome these issues for patients at high stroke risk. This paper discusses the clinical context of the application of this therapy and reviews the current experience with the AMPLATZER Cardiac Plug, a dedicated device for percutaneous LAA occlusion.

Stroke and Atrial Fibrillation

Incidence of Stroke — Stroke occurs at an annual rate of about 0.2% or at an incidence of more than 1.4 million strokes each year in the US and Europe (1)(2). The vast majority of these strokes are ischemic. Associated with a high mortality, especially within the context of atrial fibrillation (3)(4), it is the third leading cause of death after heart disease and cancer (5). Stroke has serious consequences, especially in the context of AF. The three months mortality after a first-in-lifetime stroke in AF patients was found to be more than 30%, compared with almost 20% in patients without AF (4). Furthermore, stroke may result in severe, long-term disability and functional impairment.

Cost of Stroke — For the US, the direct medical cost of stroke in 2007 was estimated to be about $25 billion and the mean lifetime cost of ischemic stroke is estimated at $140,000 per patient (1). In 2005 the total cost related to stroke in Europe was estimated at almost €22 billion, which is about one quarter of all costs related to neurological diseases and about 6% of the total budget spent on all brain disorders (6)(7).

Risk Factors for Stroke — Overall, AF is associated with a fivefold increase in stroke risk (8). The AF related stroke risk increases with age and with coexisting cardiovascular diseases. The CHADS2 risk assessment scheme (9)(10) estimates the risk for stroke in patients with AF based on well established risk factors, including cardiac failure, hypertension, age over 75 years and diabetes (contributing one point to the risk score) and previous stroke or transient ischemic attack (TIA, contributing two points). The more recently developed CHA2DS2-VASc risk assessment scheme (11) assigns two points to age ≥ 75 years and previous stroke, TIA or thromboembolism and one point each to congestive heart failure or left ventricular dysfunction, hypertension, diabetes, vascular disease, age between 65 and 74 years and sex category (i.e. female sex).

Antithrombotic Therapy in Atrial Fibrillation Patients

Stroke Prevention by Warfarin — The first therapy of choice for prevention of stroke in AF patients is antiplatelet therapy or OAC. The current ESC guidelines for management of AF (12) recommend OAC for patients with a CHA2DS2-VASc score of 1 or higher, implying that all patients with at least one risk factor are indicated for OAC.

Warfarin, one of the most commonly applied drugs for OAC, reduces the risk for ischemic stroke in AF patients by 65% (13)(14)(15)(16)(17) and is more effective than antiplatelet therapy in the prevention of ischemic stroke (18). Due to the perceived bleeding risk, the need for regular INR monitoring and dose adjustments and patient's incompliance, warfarin is used in clinical practice in only 15 to 44% of patients indicated for OAC (19)(20)(21)(22)(23). Older patients are less likely to receive OAC and are more
frequently on antiplatelet therapy (24). When receiving warfarin, patients often appear to have an INR outside the therapeutic window (25). As a result, effective stroke prevention by OAC therapy, as demonstrated in clinical trials and underlined by the guidelines, is not always achieved in clinical practice.

Warfarin has many interactions with concomitant medication and diet. In combination with a rather narrow therapeutic window this calls for regular INR monitoring. This requirement puts a heavy burden on patients as well as on healthcare providers, and may cause a conservative attitude as to the initiation or continuation of warfarin therapy. Moreover, for an individual patient the risk-benefit analysis is often complicated because many clinical conditions typical for AF patients increase the risk for stroke as well as for bleeding.

**New OAC Drugs** — In order to overcome the drawbacks of warfarin, new drugs have been developed with less dietary and pharmacological interactions and less stringent requirements for frequent INR monitoring. Results from recent trials on new drugs for OAC are summarized in Table 1. Dabigatran and rivaroxaban are at least non-inferior to warfarin in the prevention of stroke. However, they are still associated with a substantial risk for bleeding and intracranial hemorrhage. Although a higher dose of dabigatran achieves better stroke protection than warfarin, it has a similar overall bleeding risk and a significantly higher risk for GI bleeding (26). Apixaban provides better stroke prevention than aspirin at a similar bleeding risk (28) and will be compared with warfarin in the ARISTOTLE trial (29).

In view of the bleeding associated with warfarin and new OAC drugs especially patients who are at high risk for stroke as well as for bleeding may benefit from alternative stroke prevention therapies.

**OAC and Bleeding**

Obviously, the most severe complications of OAC are major bleeding and hemorrhagic stroke. Typical annual rates for major bleeding and intracranial hemorrhage in AF patients receiving OAC are reported to be 1.2% and 0.5%, respectively (30)(31). OAC associated bleeding risk increases with age, as shown by Hylek et al (32). These authors also reported on a high incidence of GI bleeding (11 out of 26 cases of major hemorrhage), an observation that was confirmed by other reports. In an analysis of 87 OAC related bleeding complications treated in the internal medicine department of a Swiss hospital (33) more than 50% of all hemorrhages and 86% of the life-threatening complications were associated with the GI tract. Especially in combination with aspirin OAC is associated with a high risk for GI bleeding (34). Specific GI bleeding risks were also underlined by the use of dabigatran in the RE-LY trial (see Table 1). Depending on the dose, the risk for GI bleeding was similar or significantly higher compared with warfarin, even if the overall bleeding risk was reduced.

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**Table 1: Randomized controlled studies on new antithrombotic medication**

<table>
<thead>
<tr>
<th>Drug/Study</th>
<th>Base Characteristics/Endpoints</th>
<th>Randomization arms</th>
<th>Effectiveness</th>
<th>Safety</th>
<th>Overall Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td><strong>RE-LY (26)</strong></td>
<td>110 mg dabigatran twice daily</td>
<td>1.53</td>
<td>2.71</td>
<td>Compared with warfarin: 110 mg dabigatran: non-inferior stroke prevention and significantly less bleeding. 150 mg dabigatran: superior stroke prevention and similar bleeding risk. 110 mg dose: similar risk for GI bleeding. 150 mg dose: significantly higher risk for GI bleeding.</td>
</tr>
<tr>
<td></td>
<td>Baseline characteristics: 18 113 pts, 71 yrs, CHADS&lt;sub&gt;2&lt;/sub&gt;: 2.1</td>
<td>150 mg dabigatran twice daily</td>
<td>1.11</td>
<td>3.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effectiveness: Stroke and systemic embolism Safety: Major hemorrhage</td>
<td>Adjusted dose warfarin</td>
<td>1.69</td>
<td>3.36</td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td><strong>ROCKET-AF (27)</strong></td>
<td>20 mg rivaroxaban daily</td>
<td>2.12 (ITT)</td>
<td>3.60</td>
<td>Rivaroxaban is non-inferior to warfarin in prevention of stroke and non-CNS systemic embolism. Major bleeding rates of rivaroxaban and warfarin are similar.</td>
</tr>
<tr>
<td></td>
<td>Baseline characteristics: 14 264 pts, 73 yrs, CHADS&lt;sub&gt;2&lt;/sub&gt;: 3.47</td>
<td>Adjusted dose warfarin</td>
<td>2.42 (ITT)</td>
<td>3.45</td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td><strong>AVERROES(28)</strong></td>
<td>5 mg apixaban twice daily</td>
<td>1.6</td>
<td>1.4</td>
<td>Compared with aspirin, apixaban provides superior prevention for stroke and systemic embolism and has similar bleeding risks.</td>
</tr>
<tr>
<td></td>
<td>Baseline characteristics: 5 605 pts, 73 yrs, CHADS&lt;sub&gt;2&lt;/sub&gt;: 2.1</td>
<td>81-324 mg aspirin daily</td>
<td>3.7</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effectiveness: Stroke and systemic embolism Safety: Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In order to quantify the risk for bleeding, risk factors have been identified and incorporated in the HAS-BLED risk assessment scheme (35). Risk factors accounted for by this scheme are hypertension, previous stroke, previous bleeding, labile INRs, and age > 65 years, all adding one point to the risk score, and abnormal renal or liver function and drugs or alcohol abuse, both adding 1 or 2 points to the HAS-BLED score. According to the ESC guidelines on management of AF (12) a HAS-BLED score of ≥ 3 indicates a high bleeding risk. The guidelines recommend regular monitoring of patients with this score, irrespective whether they are receiving warfarin or aspirin.

OAC is the first therapy of choice for stroke prevention in AF patients. Warfarin is difficult to manage, carries the risk for hemorrhagic complications, and is often used at a subtherapeutic level or not prescribed although indicated. New OAC drugs provide similar or better stroke prevention than warfarin but are still associated with bleeding complications, especially with GI bleeding.

The HAS-BLED risk assessment scheme estimates the bleeding risk based on a number of established risk factors. Some of these risk factors also increase the stroke risk in AF patients, underlining the complex risk-benefit analysis with respect to initiation of OAC therapy.

Percutaneous LAA Occlusion

**Stroke and the LAA** — The left atrial appendage appears to be the predominant location of atrial thrombus formation in patients with non-rheumatic AF (36)(37). Based on its role in cardioembolic events surgical exclusion of the LAA emerged as a therapy to prevent AF related stroke (36)(37)(38)(39). Currently, surgical resection of the LAA is recommended for patients undergoing mitral valve surgery (40).

**Percutaneous Occlusion of the LAA** — Sievert et al. (41) were the first to report on occlusion of the LAA by means of a catheter based technique. The procedure involves puncturing of the femoral vein, introduction of a catheter mounted with the collapsed occlusion device into the right atrium, transeptal entry of the left atrium (LA) and deployment and fixation of the device in the LAA orifice

Following the first clinical application, a number of devices for percutaneous LAA occlusion have been developed: the PLAATO system (eV3 Inc, Plymouth, MN, USA, no longer available), the Watchman LAA system (Atritech Inc., Plymouth, MN, U.S.A) and the AMPLATZER Cardiac Plug (ACP, St. Jude Medical, Plymouth, MN, USA). Patients treated with this technique showed a lower stroke rate than expected based on their risk profile (42)(43)(44)(45)(46), demonstrating the proof of the concept. Results of a randomized controlled study (49) showed that percutaneous LAA occlusion and subsequent discontinuation of OAC was non-inferior to warfarin therapy in the prevention of stroke, cardiac death and systemic embolism. There were more safety events in the device arm compared with the warfarin arm, and most of them were related to periprocedural complications.

**Procedural Success and Safety**

Until now reports have been published or presented on six series of patients in which the AMPLATZER Cardiac Plug was applied for percutaneous LAA occlusion (Table 2). These studies were primarily conducted to assess the performance and safety of the device during implantation, and long term follow-up data with respect to clinical outcome of the therapy was not consistently collected.

The first large cohort was reported on by Park et al. (50), including data from ten European centers.

![Figure 1: The AMPLATZER Cardiac Plug (ACP) positioned in the LAA by the dedicated delivery system.](image-url)
This data was collected retrospectively and reflects the initial experience of each center with the device in a consecutive series of patients. In a dual center study (51) the implantation of the device with and without transesophageal echocardiography (TEE) was compared. The study was conducted in two centers that gained experience on the device and its implantation in the initial European registry. The ACP Prospective Multicenter European Registry (52) is currently ongoing and is aimed at enrollment of 200 patients. Recently presented interim data on 145 patients is included in Table 2. Only 3.3% of the study cohort was on OAC at device implant, whilst 91% had a known bleeding history or had a contraindication to OAC. The implant success rate was 96.5% and closure rate 99%, and a favorable adverse event rate, which compares favorably with other devices and is consistent with previous ACP publications. This patient population is ‘sicker’ in this study, given the higher CHADS2 score, older, predominantly permanent AF, patients not tolerable to anticoagulation. The Italian registry (53) prospectively collected data in 17 centers from their initial population of consecutive AF patients, considered candidates for percutaneous LAA occlusion. Prior to commencing application of the device, the operators involved in this study were intensively trained by physicians experienced with the device and the implantation procedure. Two other reports describe the initial experience with the device obtained from a single center in Israel (54) and from two centers in the Asian-Pacific region (55).

In summary, patients included in these studies had a history of AF, were at medium to high risk for stroke and contraindicated for OAC. Contraindications were usually due to gastrointestinal bleeding, intracranial bleeding, poor compliance and frequent falls. The implant procedures were performed under fluoroscopy and usually under TEE, except for the dual center study comparing implantation with and without TEE (51). In the majority of procedures, access to the left atrium was achieved by transeptal puncture (85% of the cases reported). In the remaining procedures, the left atrium was reached by means of a patent or reopened foramen ovale or through an atrial septal defect.

The reasons reported for not attempting LAA occlusion were the inability to reach the atrial septum, either due to abdominal situs inversus or a missing inferior vena cava, the presence of thrombus in the LAA or conditions related to the LA/LAA anatomy.

In the cumulative cohort of 577 patients enrolled for these six studies and 569 patients in whom percutaneous LAA occlusion was attempted, the device was successfully implanted in 555 patients (97.5% of the attempts). Failure to implant the device, reported in 14 cases, was most commonly due to a difficult anatomy of the LAA. Other reasons preventing successful implantation were embolization of the device and catheter related thrombus both causing abandonment of

### Table 2: Studies on procedural success and safety of percutaneous LAA occlusion with the ACP device

<table>
<thead>
<tr>
<th>Study</th>
<th>Park et al. (50)</th>
<th>Park et al. (51)</th>
<th>Park (52)</th>
<th>Santoro et al. (53)</th>
<th>Meerkin et al. (54)</th>
<th>Lam et al. (55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of centers</td>
<td>10</td>
<td>7</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CHADS2</td>
<td>3</td>
<td>2.6</td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients enrolled</td>
<td>143</td>
<td>135</td>
<td>100</td>
<td>100</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>LAA occlusion attempted</td>
<td>137</td>
<td>133</td>
<td>140</td>
<td>34</td>
<td>99 (99.0%)</td>
<td></td>
</tr>
<tr>
<td>Successful LAA occlusion</td>
<td>132 (96.4%)</td>
<td>131 (98.5%)</td>
<td>140 (96.5%)</td>
<td>99 (99.0%)</td>
<td>34 (100%)</td>
<td>19 (95.0%)</td>
</tr>
<tr>
<td>&gt; 1 device</td>
<td>25 (18.2%)</td>
<td>7</td>
<td>7</td>
<td>10 (10.0%)</td>
<td>8 (23.5%)</td>
<td></td>
</tr>
<tr>
<td>Major periprocedural</td>
<td>10 (7.3%)</td>
<td>0 (0.0%)</td>
<td>5 (3.4%)</td>
<td>1 (1.0%)</td>
<td>1 (2.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Device embolization</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac perforation/effusion</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Minor periprocedural</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Notes:

* Interim data presented on 145 patients; target enrollment is ≥ 200 pts.
* Patients enrolled: number of patients considered for percutaneous LAA occlusion.
* LAA occlusion attempted: number of patients in whom the left atrium was successfully accessed and LAA occlusion was attempted.
* All percentages are related to the number of occlusions attempted.
* > 1 device: number of procedures in which the initially selected device was exchanged for a second or third device.
the procedure. All embolized devices were successfully retrieved.

As far as reported, in 84% of the procedures the device that was initially selected following angiographic and echocardiographic assessments could be successfully implanted. In the remaining procedures the initial device had to be exchanged for a smaller or larger device to adapt to the LAA dimensions. In the initial European registry (50) devices had to be exchanged more often than in the Italian registry (53), in which operators were trained based on earlier experiences. Furthermore, regarding their cohort of 34 patients, Meerkin et al. (54) noted that 6 out of the 8 device exchanges occurred in the first 9 procedures.

Major complications were reported from 17 procedures, including stroke (n = 3), device embolization (n = 4) and cardiac perforation and/or significant pericardial effusion, requiring pericardiocentesis (n = 10). In all cases of significant effusion the event was resolved without remaining sequela. As is obvious from the data presented in Table 2, the majority of major periprocedural events (10 out of 17) was observed in the early report on initial European experience (50).

Almost half of the minor complications reported also occurred in the initial European registry (50). Minor complications included insignificant pericardial effusion not requiring intervention, thrombus formation on the device, transient coronary embolism or myocardial ischemia and hematoma at the venous access site. In addition, in one case the implant was lost in the venous system and could successfully be retrieved. In another case, TEE associated esophageal injury occurred.

Of note with regard to procedural experience with the ACP device is that the dual center study comparing implantation with and without TEE guidance concluded that both procedural strategies allow for safe implantation of the device (51).

With regard to the initial Asian-Pacific experience (55), no stroke, transient ischemic stroke or systemic embolization was observed at a mean follow-up of 12.7 months. Patients in the initial European registry (50) will be followed to assess the clinical efficacy of the therapy at longer term.

Percutaneous LAA occlusion has emerged as an alternative to OAC for AF patients at high risk for stroke who are contraindicated for anticoagulation. (56) Cumulative experience with the ACP device shows high procedural success rates and, except for the initial cases, low periprocedural complication rates. The most common procedure related safety event is pericardial effusion, occurring less frequently with increasing operator experience.

Discussion and Conclusion

Percutaneous LAA occlusion has shown to be effective in the prevention of stroke in AF patients. This therapy reduced the stroke rate compared with the CHADS2 predicted rates (42)(43)(44)(45)(46) and first evidence regarding the non-inferiority of percutaneous LAA occlusion compared with warfarin has been reported (49). Based on successful stroke prevention, LAA occlusion may eliminate the need for OAC and prevent OAC associated bleeding events. Although this benefit may be offset by complications related to the implantation of the device, this review has shown that periprocedural complications occur less frequently with increasing operator experience.

Initial experience with the ACP device (50) showed a periprocedural complication rate of 7%. This result was achieved in ten European centers that started application of the new device without prior clinical experience regarding the specific device. In more recent studies existing experience with the device could be applied and operators were trained using clinical observations and procedural experience gained by other physicians. As illustrated by the data in Table 2 these more recent studies showed a marked reduction in the number of procedure related safety events compared with earlier initial experiences. Moreover, operators new to the device noted that most of the periprocedural complications occurred in the early procedures. Comparing results obtained during initial experience with the device (49) (53)(54) with those from more experienced or intensively trained operators (50)(51)(52) shows a marked reduction in the major periprocedural complication rate from 5.8% for initial application of the device to 1.6% at a very experienced stage.

The learning curve effect observed in the application of the AMPLATZER Cardiac Plug device is confirmed by results reported on other devices (57).

In conclusion, as with every interventional procedure, percutaneous LAA occlusion with the ACP device shows an obvious learning curve effect. After appropriate operator training and gaining initial experience, implantation of the device is safe and a high procedural success rate can be achieved.
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