National Institute for Health and Clinical Excellence

310/2 –Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

Consultation Comments table

IPAC date: Thursday 15th April 2010

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1	Consultee 1 NHS Consultant Cardiologist	**1**	I am not sure that a cardiac surgeon needs to be involved in the selection process as no one is going to be recommending surgery as an alternative treatment. Â Surgical input might be needed in the event of complications such as effusion and tamponade or occluder embolisation. Â Unlike ASD or VSD closure where surgery is an alternative treatment and it is important to have surgical input for LAA occlusion and PFO closure the alternative treatment is medical therapy and surgical input is only needed to deal with complications if they arise. It might make more sense to have input from stroke physicians, neurologists or haematologists as they are the clinicians most likely to offer an alternative treatment.	Thank you for your comment. The guidance will be changed in section 1.2 to 'Patient selection should be carried out by a multidisciplinary team including a cardiologist *and other appropriate physicians experienced in the management of patients with atrial fibrillation at risk of stroke*.'
2	Consultee 2 Cardiologic, Ltd	**1**	1.5. This is a potentially high risk procedure and the database should be in place to record all implants before or at time of approval. As learning curve complications will need to be monitored and disseminated.	Thank you for your comment. The guidance will be changed. Section 1.5 (referring to the UK Central Cardiac Audit Database) has been deleted. A new section 1.5 has been added stating: '*Any device-related adverse events resulting from the procedure should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA)*.'

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3	Consultee 3 Atrial Fibrillation Association	**1**	I think the recommendations are fair. Â It may be sensible to reccomend that people implanting this device (who have not got signficant experience of the device) should be physicians with a large experience of transeptal puncture and intrumentation of the left atrium. Given that there are a large body of physicians with this type of skill (e.g. those performing AF ablation) it would seem to expose patients to unecessary risk to have physicians without this experience performing this procedure. My only criticism is the insistance that a multidisciplinary team decide on patient selection. There is nothing a surgeon is going to bring to the table in many cases and this is an unnecessary requirement.	Thank you for your comment. The guidance will be changed in section 1.2 to 'Patient selection should be carried out by a multidisciplinary team including a cardiologist *and other appropriate physicians experienced in the management of patients with atrial fibrillation at risk of stroke*.' The guidance will also be changed in section 1.3 to 'Percutaneous occlusion of the LAA is a technically challenging procedure which should only be carried out by clinicians with specific training *and appropriate experience*.'
4	Consultee 4 NHS professional	**1**	These recommendations are entirely correct. One addition I think should be made - it is clear that there is "interest", at both the appropriate and inappropriate level - from both District General Hospitals and Electrophysiologists with NO TRAINING in either PFO, ASD, VSD or other device deployment. The LAAO is a technically difficult procedure. It requires careful handling of large calibre catheters in a friable structure. As such, it is in my view wholly inappropriate at this stage that anyone should be doing this procedure who does not have significant experience in the use of devices to close atrial communications. I think this factor should be made explicit in the guidance.	Thank you for your comment. The guidance will be changed in section 1.3 to 'Percutaneous occlusion of the LAA is a technically challenging procedure which should only be carried out by clinicians with specific training *and appropriate experience*.'
5	Consultee 5 AGA Medical	**1**	The complications noted have been reduced with operators learning experience. Â AGA Medical's vigilance reporting supports this observation revealing an exponentially decreased number of reportable adverse events with increased implant experience (reflected by cumulative number of implants performed). Â Data is on file at AGA Medical.	Thank you for your comment. The guidance will be changed in section 1.3 to 'Percutaneous occlusion of the LAA is a technically challenging procedure which should only be carried out by clinicians with specific training *and appropriate experience*.'
6	Consultee 6 NHS Professional	**1**	It is unclear why the multidisciplinary discussion of these cases specifically requires the input of a cardiac surgeon. Â It might be more relevant to require discussion with a non-interventional cardiologist who could provide an unbiased opinion about alternative treatments. Â In addition the discussion should include expertise in transoesophageal echocardiography as this is a critical part of the procedure.	Thank you for your comment. The guidance will be changed in section 1.2 to 'Patient selection should be carried out by a multidisciplinary team including a cardiologist *and other appropriate physicians experienced in the management of patients with atrial fibrillation at risk of stroke*.'

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7	Consultee 7 NHS Professional Specialist Adviser	**1**	Centres performing this procedure require the involvement of a cardiac surgeon in case of the need for emergency surgery. Â Patient selection however, does not routinely require surgical input as there is no good surgical alternative. Selection requires expertise from physicians in the assessment of procedural risk vs. risk of embolic stroke and haemorrhage from anti-coagulant therapy.	Thank you for your comment. The guidance will be changed in section 1.2 to 'Patient selection should be carried out by a multidisciplinary team including a cardiologist *and other appropriate physicians experienced in the management of patients with atrial fibrillation at risk of stroke*.'
8	Consultee 1 NHS Consultant Cardiologist	**2.1**	It is worth including that LAA closure may be indicated if the risks of alternative treatments are considered higher- such as bleeding complications related to warfarin anticoagulation. Â Those with active lifestyles which includes activities that might be associated with head injury and subsequent bleeding (e.g horse riding) might also wish to choose LAA closure in preference to lifelong warfarin anticoagulation.	Thank you for your comment. This guidance is for LAA closure in the context of non-valvular atrial fibrillation only and the factors referred to here would be important in the decision making of the MDT.
9	Consultee 2 Cardiologic, Ltd	**2.1**		The consultee's comments related solely to the claimed benefits of thoracoscopic epicardial closure of the LAA, referring to brand names. The comments have therefore been removed from the consultation table before publication,
10	Consultee 5 AGA Medical	**2.1**	Observations From the evidence used, there is one RCT (WATCHMAN) and all others are case studies pertaining to PLAATO device. NICE does recognize the use of AMPLATZER Cardiac Plug (ACP) in the specialist Adviser Opinion section. Recommendation • ACP- The AMPLATZER Cardiac Plug was approved in (September 10, 2008) is a percutaneous transcatheter device intended to prevent thrombus embolization from the left atrial appendage (LAA) in patients who have non valvular atrial fibrillation. • WAATCHMAN- Â The WAATCHMAN device is indicated for patients with paroxysmal, persistent, or permanent non-valvular Afib who are eligible for long term warfarin therapy • All other case studied reported (PLAATO experience)- Patients with non-valvular Afib and contraindication for anticoagulation therapy	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

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11	Consultee 4 Specialist adviser	**2.2**	It is important at this stage that the word "MAY" (2/2/1)is excluded. "Patients SHOULD have the procedure undertaken under general anaesthsia with transoesophageal echocardiographic control" would be a more appropriate statement. To undertake the procedure without online TOE would be negligent in my view - there is NO WAY of identifying that the device is adequately placed without intraprocedure TOE.	Thank you for your comment. The guidance will be changed in section 2.2.1 to state: 'The location of the LAA is confirmed and the size of the LAA orifice ***is*** established by transoesophageal echocardiography.'
12	Consultee 5 AGA Medical	**2.2**	• Percutaneous procedure very similar to other transcatheter cardiac procedures such as cardiac angiograph/stent, cardiac ablation procedure	Thank you for your comment
13	Consultee 5 AGA Medical	**2.2**	• Transeptal access – similar technique used in ablation procedures. Patient population being considered for percutaneous LAA closure may undergo ablation procedures with involved risks of transeptal even if they were not having a percutaneous LAA closure	Thank you for your comment.
14	Consultee 5 AGA Medical	**2.2**	• Procedure Less invasive procedure in comparison to surgical ligation of LAA	Thank you for your comment.
15	Consultee 5 AGA Medical	**2.2 cont**	• Percutaneous device is repositionable and retrievable	Thank you for your comment.
16	Consultee 5 AGA Medical	**2.3**	Observations RCT data (707 patients) reports • All stroke rate of 2.3 per 100 patient years in the intervention group out of which the ischemic and hemorrhagic stroke rates are 2.2 and 0.1 per 100 patients years respectively. . It must be noted (as stated in footnote a, page 6 of 38) that all patients who had an ischemic stroke had sub therapeutic INRs. Also, one of these strokes occurred following randomization but before device closure. This may imply that there have been other contributing factors for causation of stroke and may not be device related.	The guidance is a summary of the evidence. The overview provides more details about individual studies.

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17	Consultee 5 AGA Medical	**2.3 cont**	• The hemorrhagic stroke rate is lower in the intervention group in comparison to the control group (0.1 vs.1.6) which is of note as it emphasizes the complication due to continued use of warfarin. It is acknowledged that the 1 patient who suffered a Hemorrhagic stroke (intervention group) occurred within 45 days after implant while taking warfarin. The occurrence of hemorrhagic stroke implies the inherent risk of bleeding associated with use of warfarin.	
18	Consultee 5 AGA Medical	**2.3 cont**	• 86% of patients discontinued warfarin at 45 days and 92% stopped by 6 months. This aligns with the objective of percutaneous device closure which serves as a viable alter	Thank you for your comment.
19	Consultee 1 NHS Consultant Cardiologist	**2.4**	The complication rates are likely to vary between the different occluders and it is anticipated that the later generation occluders which are more flexible may have lower serious complication rates though this is still to be fully proven.	The IP Programme issues guidance on a procedure and does not compare individual devices. Section 2.5.1 includes a note from the Committee, highlighting that clinical outcomes may be different in the available devices.
20	Consultee 4 Specialist adviser	**2.4 cont**	These data confirm why the procedure MUST be undertaken in units with onsite cardiothoracic surgery. There is no rationale for undertaking these elective procedures in units which do not have this expertise immediately available.	Thank you for your comment. (Consultee agrees with section 1.4)
21	Consultee 5 AGA Medical	**2.4 cont**	ECONOMIC IMPACT Published literature to date indicates that stroke and the requisite long term care following a stroke may account for as much as 3–5% of all national health care expenditures in many countries. Â If a safe and effective stroke prevention alternative therapy could be made available, a substantial lifetime cost savings could be realized and the impact to the UK health care economy would be significant (Miller et al).	Cost-effectiveness is not part of the remit of the IP Programme.

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22	Consultee 5 AGA Medical	**2.4 cont**	AMPLATZER CARDIAC PLUG – POST MARKET REGISTRY AGA Medical has initiated a post-market clinical registry with the AMPLATZER Cardiac Plug (ACP) in centers across Europe. Â The registry is a prospective, open label, non-randomized evaluation to evaluate the performance of the ACP device in the closure of the LAA in approximately 200 patients with paroxysmal, non-valvular atrial fibrillation. Â The performance of the ACP will be compared versus published data of comparator devices (Watchman and Plaato) with the results disseminated through major publications and scientific congresses.	Thank you for your comment.
23	Consultee 5 AGA Medical	**2.4 cont**	ADDITIONAL DATA AGA Medical recommends including the following abstract in the APPENDIX A of the proposed NICE guidance document – International Congress of Cardiology 26-28th February 2010. LAA closure with the Amplatzer Cardiac Plug for the prevention of stroke in afib – initial European experience – JW Park et al.The abstract reports the initial European experience with the ACP device for LAA closure. The abstract was presented at the International Congress of Cardiology, Hong Kong (February 2010). Â It is acknowledged that this abstract does not currently serve as evidence in formulating the guidance due to the following reasons: • Retrospective analysis of data • Abstract is not peer reviewed	Thank you for identifying this abstract. The consultee refers to an abstract which is not peer-reviewed. The NICE IP Methods Guide highlights that efficacy outcomes from abstracts and non-peer reviewed sources are not normally presented to the Committee.
24	Consultee 5 AGA Medical	**General**	Other comments not necessarily related to safety Risk Benefit Assessment The Guidance document provides details of available evidence and highlights the safety and efficacy details of percutaneous device occlusion. For meaningful interpretation of this information it may be important to put this data into context with information on alternative therapies which then may provide a complete representation of the risk benefit profile of device occlusion. Stroke is the third leading cause of mortality in the developed world 1 Each year, approximately 795 000 people experience a new or recurrent. 2 Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and its' association with stroke is well known. In patients with Non Rheumatic AF (NRAF), 91% of LA thrombi were found in the LAA. 3 Previous observations have demonstrated that most embolic phenomena were associated	Both the overview and guidance are intended only to give brief descriptions of the indications and current treatment.

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			with LAA thrombus in patients with AF. 4,5 Therefore, it appears that treatments that obliterate the LAA may reduce stroke risk in AF. Certain therapies are available to reduce the risk of stroke associated with AF. Described below are therapies available to reduce AF-associated stroke risk and its'inherent risks in comparison to the novel approach of percutaneous left atrial appendage (LAA) exclusion provided by the ACP device? The frequency of AF in the general population has been estimated to be 0.9%. 6 The rate of ischemic stroke among patients with non-rheumatic AF averages 5% per year, 7,8 a 5- to 6-fold excess risk of stroke independent of other factors. 9 NRAF is responsible for 18–29% of all ischemic strokes, 10,11 and conversely, as many as 20% of all ischemic strokes occur in patients with AF.9,12 The frequency of AF in patients admitted for a first-ever stroke increased from 3.8% in those Â 50 years of age to 34.3% in those ≥ 90 years of age.11 Cardio embolic strokes account for approximately 20% of all ischemic strokes, with AF — responsible for about 50% of all cardiac emboli — being the most common cause of cause of cardiogenic embolism.13 More importantly, patients with stroke and AF tend to be more severely disabled on admission and have a 50% increased mortality and greater disability at 3 months, independent of other baseline risk factors. 10,11 Oral anticoagulation (OAC) has been shown to reduce stroke risk in patients with AF by 62–68%,8 and is currently the most effective preventive therapy for this group of patients. Although the benefit of anticoagulant therapy in preventing thromboembolic events was clearly shown through several studies, a significant number of patients with atrial fibrillation do not receive anticoagulant therapy. The underutilization of warfarin therapy may either be due to the presence of contraindications or due to reasons such as associated bleeding complications, non compliance, physician's prescribing practices, impairment of quality of life etc in patients who are eligible to take warfarin. It has been estimated that approximately 17%23 of patients are	

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			contraindicated to take warfarin. There have been no randomized trials with distinct follow-up on this cohort of patients to determine their risk of events or mortality. However, the risk profile may be predicted to be similar to the subset of AF patients who are eligible but do not receive any antithrombotic therapy. The rate of events such as all strokes, Transient Ischemic attack, systemic embolism, myocardial infarction has been estimated to range from 9.8% to 17 % 14,24,25 and Â the mortality rate ranged from 6% to 24% 24,25. In addition to the group of patients who are contraindicated to take antithrombotic medications, there are a significant proportion of AF patients who are risk for stroke and eligible to take warfarin but not receive the therapy. In clinical practice oral anticoagulants are prescribed to only 15% to 66% 26 of patients with AF at high risk of thromboembolic events and no clear contraindication. Analysis of the National Ambulatory Medical Care surveys showed that the use of warfarin ranged from 3%-20% between 1980-85 and increased to 35-40%between 1993-1996. From 1996-2000 this survey estimated the use of warfarin in patients with AF to be only 40%-50%. 27,28 Â Warfarin therapy has a narrow therapeutic window, requires frequent blood sample monitoring, has significant drug-to-drug interactions, and increases the risk of bleeding, especially in the elderly, and some patients may simply be unable to maintain a stable INR. Previous studies indicate that the risk of stroke rose steeply at INRs Â 2.0, while the risk of hemorrhage increased rapidly at INRs Â 4.0.15,16 Major bleeding was reported to occur in 6.5% of patients per year, with age ≥ 65 years, history of gastrointestinal bleeding or stroke being independent risk factors. 17 In a recent study, elderly patients (≥ 80 years old) who are at the highest risk of stroke had a major hemorrhage rate of 13.1% compared to 4.7% in those Â 80 years of age.18 Within the first year, 26% of these elderly patients stopped taking warfarin, with safety issues the perceived reason in 81% of them.18 It can therefore be concluded that despite oral anticoagulation therapy for patients with AF being established as an effective therapy,	

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			there are several limitations to its' use and in these patients the ACP is a viable alternative? Â There is an additional unmet clinical need in the Â subset of patients in whom OAC is indicated but not taken for the reasons described above. Surgical exclusion- Surgical techniques are used to close the LAA include excising or excluding the appendage. Excision is performed by removal of the LAA, either by scissors or an amputating stapling device. Excision is performed by closing the orifice into the LAA cavity with the appendage remaining attached. In a retrospective review of 205 patients (58/205 underwent ligation), the risk of stroke was found to be significantly reduced in patients who underwent LAA exclusion during mitral valve (MV) replacement compared to those who did not(27 patients had embolic events).4 However, there are no randomized data and an observational study actually showed a higher subsequent stroke rate in patients who had LAA exclusion during MV surgery if warfarin was stopped than if it was continued, suggesting that LAA exclusion itself may provide inadequate stroke prevention.19 Exclusion of the LAA during cardiac surgery can be safely performed either with sutures or staples20 . Incomplete exclusion of the LAA, however, has been reported in 36–55% of patients. 20,21 The presence of LAA thrombus has been documented in these partially-excluded LAAs, and may account for observed thrombo-embolic phenomena.21 Surgical exclusion is an invasive procedure, and is most often performed during valve surgery or during Maze procedures. It can therefore, be concluded that surgical ligation of LAA is a not routinely performed as an elective procedure. It is performed as an adjunct to another major cardiac procedure such as MAZE thereby exposing these patients to the inherent surgical risks of open thoracotomy. Radiofrequency ablation of A-fib - Â Patients with AF may undergo percutaneous Radiofrequency ablation As AF has been observed to be initiated by ectopic beats originating from atrial tissue within the pulmonary veins. Though catheter ablation procedures have been shown to be successful and this procedure does not involve exclusion of LAA, it may serve to compare the safety profile with	

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			percutaneous device closure of LAA due to the common access technique and its associated complications (transeptal puncture). A meta-analysis by Cappato et al reported a major complication rate of 6.0% (Cappato, 2005) 22. The most significant complications included: • Periprocedural death (0.05%) • Tamponade (1.22%) • Sepsis, abscesses, or endocarditis (0.01%) • Pneumothorax (0.02%) • Hemothorax (0.16%) • Permanent diaphragmatic paralysis (0.11%) • Femoral pseudo aneurysm (0.53%) • Arterovenous fistulae (0.42%) • Valve damage (0.01%) • Aortic dissection (0.03%) • Stroke (0.28%) • Transient ischemic attack (0.66%) • Stenosis of pulmonary veins (1.3%) In conclusion, catheter based ablation has its underlying associated risks as described above. Additionally, these patients may be subjected to reintervention procedures which increases their exposure to the risks involved. Cappato et al reported a reintervention rate of 24.3 % of patients requiring a second reintervention for RF ablation and 3.1% requiring a third intervention. Ablation procedures may not serve as an alternate treatment option as it has been reported through a largest series of AF ablation that OAC was recommended to continued for 3 -6 months after the ablation procedure 29 . Conclusion AF is a well-known predisposing factor for stroke, raising the risk significantly. It has been documented that the LAA is the main source of LA thrombus, especially in NRAF. Alternative therapies to treat either AFib or closure of LAA exists but are not without associated complications. Oral anticoagulation with warfarin is the most effective therapy for stroke risk reduction however, this therapy increases the risk of bleeding and is often underutilized, contraindicated, or when administered, often sub therapeutic. Â Retrospective studies have demonstrated that surgical LAA exclusion may reduce the risk of stroke and embolic events in AF patients. Although these techniques are simple to apply, there is uncertainty regarding its effectiveness and reproducibility. Additionally, since surgical exclusion of LAA is mostly performed in association with other cardiac procedures, there are inherent surgical risks involved. AFib patients routinely	

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			undergo catheter ablation procedures which involve similar access technique of transeptal puncture as involved in percutaneous closure of LAA {end} In reviewing the alternative therapies in terms of benefits and risks and compared to the reported benefits and risks of percutaneous device closure, the following conclusions can be drawn which indicate that the benefits involved with percutaneous device closure of LA outweigh the risks: **1.** Percutaneous device closure has been shown to reduce the risk of stroke and embolic events **2.** The procedural risks and therefore patient exposure to these risks may be no different than if they underwent ablation procedures. **3.** Percutaneous device exclusion potentially limits the need for long term continuation of warfarin and therefore alleviates the inherent risks and quality of life impact associated with warfarin usage- namely , bleeding risks, drug interactions, lifestyle modifications, periodic INR monitoring. **4.** Device closure offers the potential benefit of shorter procedure time and recovery in comparison to surgical exclusion procedures especially since LAA ligation is associated with other major procedures such as MAZE procedures. **5.** The rates of procedural risks for device closure such as pericardial effusions/tamponade Â are comparable to other cardiac surgical and EP procedures which range from 1-5% **6.**Percutaneous device occlusion is a permanent implant and reintervention has not been reported,whilst with surgical and radiofrequency ablation, reintervention may be necessary Cappato et al reported a reintervention rate of 24.3 % of patients requiring a second reintervention for RF ablation and 3.1% requiring a third intervention. Â Pharmacological therapy is life long treatment and , warfarin safety is highly dependent upon close and regular medical monitoring, and has potentially serious side effects **7.** Despite the available treatment options for AF patients there	

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			remains a significant proportion of patients in whom percutaneous device closure may provide a valuable alternative to patients contraindicated for/or not complying with life long OAC therapy.	

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