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CONSENSUS DOCUMENT

Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies

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The increasing interest in left atrial appendage occlusion (LAAO) for ischaemic stroke prevention in atrial fibrillation (AF) fuels the need for more clinical data on the safety and effectiveness of this therapy. Besides an assessment of the effectiveness of the therapy in specific patients groups, comparisons with pharmacological stroke prophylaxis, surgical approaches, and other device-based therapies are warranted. This paper documents the consensus reached among clinical experts in relevant disciplines from Europe and North America, European cardiology professional societies, and representatives from the medical device industry regarding definitions for parameters and endpoints to be assessed in clinical studies. Adherence to these definitions is proposed in order to achieve a consistent approach across clinical studies on LAAO among the involved stakeholders and various clinical disciplines and thereby facilitate continued evaluation of therapeutic strategies available.

Keywords Atrial Fibrillation • Stroke • Prevention • LAA closure

Introduction

Left atrial appendage occlusion (LAAO) is a device-based therapy for stroke prevention in patients with non-valvular atrial fibrillation (AF), which continues to evolve. Important issues remain to be clarified including the outcome and safety of this local site-specific therapy vs. systemic anticoagulant therapy, comparison of the multiple approaches being studied, the specific patient population and risk benefit ratio in these populations as well as the long-term follow-up. These clinical initiatives will benefit from standardization of definitions that

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will enhance the ability to make meaningful comparisons of the safety and efficacy of the diverse approaches available.

The present document is the output of a 2-day consensus conference that was organized on 28–29 August 2014 in Munich, Germany. It is complimentary to the European Heart Rhythm Association / European Association of Percutaneous Cardiovascular Interventions consensus document[1] by providing definitions for the parameters and characteristics assessed for LAAO and other stroke prevention therapies compared with LAAO. Within the field of interventional cardiology, the consensus documents published by the Valve Academic Research Consortium (VARC)[2,3] significantly contributed to the use of consistent definitions for research purposes. Where meaningful, these definitions have been adopted within this document, with modifications relevant to specific aspects of LAAO, such as venous access and transseptal puncture.

Atrial fibrillation, stroke, and left atrial appendage occlusion

In a typical cohort of non-treated non-valvular AF patients, the annual rate of ischaemic stroke is ~5%, although much higher-risk populations for thromboembolism and for bleeding can be identified using risk scores such as CHA_2DS_2-VASc (or $CHADS_2$) and HAS-BLED.[4] Oral anticoagulation (OAC) with vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs) has been demonstrated to significantly reduce this risk of stroke or systemic embolism by >60%.[5,6] However, VKA therapy is associated with clinically relevant bleeding.[4,5] Non-VKA oral anticoagulants less frequently result in OAC-associated life-threatening bleeding,[6] but major bleeding may not be less than with VKA therapy, and gastrointestinal bleeding has often been more pronounced with NOACs, which therefore may not be the preferred therapy for AF patients with a high bleeding risk. The overall bleeding risk as a drug class may be lower with NOACs compared with warfarin, but it is not zero. Moreover, other AF patients have absolute contraindications to pharmacological stroke prophylaxis or may suffer a systemic thromboembolisation event despite adequate OAC accounting to 'failed therapy'. The finding that 91% of thrombi in this setting originate in the left atrial appendage (LAA)[7] constitutes the rationale for stroke prevention by exclusion of the LAA as applied using several therapeutic approaches. Surgical approaches include the total excision of the LAA or exclusion by ligation or stapling[8,9] as well as epicardial clips applied to close the LAA after obtaining access by sternotomy or less invasive thoracoscopic approaches.[10,11] While these surgical approaches are applied with variable success, they are highly invasive techniques and particularly surgical excision or exclusion is done concomitantly along with surgical AF ablation, valve repair/replacement, or coronary artery bypass grafting.

While percutaneous LAAO was initially developed to replace OAC, in Europe and most recently in North America, it is currently considered for non-pharmacological stroke prevention in AF patients in whom long-term OAC is not considered a first-choice therapy.[12–15] The ESC guidelines for the management of AF[16] recommend that interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term OAC (Class IIb, Level B). Surgical excision of the LAA may be considered concomitantly in AF patients undergoing open-heart surgery (Class IIb, Level C). The same recommendations are included in the ESC/EACTS guidelines on myocardial revascularization with respect to patients with AF undergoing percutaneous coronary intervention or coronary artery bypass grafting.[17] The US guidelines do not supply any recommendation because until very recently none of the LAAO devices had been approved in the USA. In March 2015, the Food and Drug Administration (FDA) announced the approval of the Watchman device.[18] The FDA stated that the Watchman device is indicated to reduce the risk of thromboembolism from the LAA in patients with non-valvular AF who (i) are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy, (ii) are deemed by their physicians to be suitable for warfarin, and (iii) have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared with warfarin. Noteworthy, while all randomized studies so far have included patients eligible for warfarin therapy, European registries and common sense in the panels have led to considering this option mainly for patients with absolute or relative contraindications for warfarin. Nevertheless, at the moment, there is no scientific consensus on the definitions of absolute or relative contraindications for OAC therapy for patients with AF, so the exact indications for LAAO have yet to be clarified.[19] Acknowledging this fact, potential indications for LAAO therapy and some common examples are provided in *Table 1*.

Percutaneous LAAO encompasses occluding the LAA with a mechanical device through a catheter-based, transseptal approach or ligating the LAA through a combined strategy requiring transvenous, transseptal, and transpericardial access. Patient cohorts, treated with this therapy, have stroke rates lower than expected based on their risk factors,[15,20] confirming the role of the LAA as the predominant origin of atrial thrombi. The randomized controlled PROTECT-AF trial[21] demonstrated the non-inferiority of LAAO with the Watchman device compared with dose-adjusted warfarin therapy in the prevention of ischaemic stroke, systemic embolism, and cardiovascular death. At a longer-term follow-up (3.8 years) of the study cohort, there was evidence of superiority in cardiovascular and all-cause mortality in comparison with warfarin.[22] Patients in this study received warfarin until appropriate LAAO was confirmed and device-related thrombus excluded by transoesophageal echocardiography (TEE) at 45 days after implantation. The randomized controlled PREVAIL study[23] failed to show the non-inferiority of LAAO with the Watchman device for overall efficacy. However, event rates in the control group were lower than expected, and LAAO was non-inferior to warfarin for ischaemic stroke or systemic embolism prevention >7 days after device implantation. Moreover, the study showed that the Watchman device could be safely implanted by new operators.

Most common complications related to the LAAO therapy are cardiac perforation, pericardial effusion, tamponade, device embolization, systemic thromboembolism, and injury related to vascular access.[24] Despite higher initial procedural complications, operators showed a positive learning curve in the implantation of the LAAO device,[25–27] with a significant reduction of complication rates to 2–3%.[26]

Recently, a hybrid approach for epicardial LAA ligation has been introduced, combining transcatheter endocardial techniques and

Table 1 Indications for LAAO therapy

Potential indications	Examples
A. Patient not eligible for long-term OAC therapy (absolute or relative contraindications to OAC)	
1. High risk for bleeding	
• History of major or minor bleeding (with or without OAC therapy)	• Intracranial bleeding • GI bleeding • Symptomatic bleeding in critical organ (i.e. ocular, pericardial, spinal cord) • Recurrent epistaxis needing medical attention
• Increased risk for bleeding due to physical condition and/or co-morbidities	• Recurrent falls with head trauma and significant musculoskeletal injury • Need for additional dual antiplatelet therapy for CAD and stenting • Diffuse intracranial amyloid angiopathy • Bowel angiodysplasia • Severe renal insufficiency/hemodialysis • Blood cell dyscrasia
2. Inability to take OACs for reasons other than high risk for bleeding	• Intolerance • Documented poor adherence to medication • Documented variability in international normalized ratio on warfarin • Higher-risk occupation with increased injury potential • Patient's choice
B. Thromboembolic event or documented presence of thrombus in the LAA despite adequate OAC therapy	• Embolic stroke or other systemic thromboembolism on adequate OAC therapy with evidence for thrombus origin from the LAA ('malignant LAA') • Documented thrombus formation in the LAA on adequate OAC therapy

OAC, oral anticoagulation; GI, gastrointestinal; CAD, coronary artery disease.

Table 2 Mortality definitions[3]

Cardiovascular mortality	• Death due to proximate cardiac cause, e.g. myocardial infarction, cardiac tamponade, worsening heart failure, and endocarditis. • Death caused by non-coronary, non-CNS vascular conditions such as pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease. • Death from vascular CNS causes ○ From haemorrhagic stroke, ○ From ischaemic stroke. • All procedure-related deaths (see definition below), including those related to a complication of the procedure or treatment for a complication of the procedure. • Sudden or unwitnessed death defined as non-traumatic, unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 h before the event. • Death of unknown cause.
Non-cardiovascular mortality	Death of a primary cause that is clearly related to another condition (e.g. trauma, cancer, suicide).
Procedural mortality	All-cause mortality during the index procedure, any procedure-related death within 30 days after the index procedure or during post-operative hospitalization for the index procedure (if >30 days).
Immediate procedural mortality	All-cause mortality <72 h after commencing the index procedure.

epicardial access by minimal invasive surgery.[28,29] While initial results showed the feasibility and safety of this technique, limited early experience similar to the other LAAO devices is going through a similar learning curve with a slightly higher rate of bleeding and cardiac tamponade in small series of patients reported in retrospective studies.[30] The efficacy and safety of this technique is yet to be fully established in larger multicentre randomized controlled studies or registries. This is particularly important for devices that have not yet been tested in randomized control trials.

Mortality

A meaningful assessment of mortality associated with LAAO should address the timing relative to the index procedure as well as the underlying causes. Mortality definitions provided in *Table 2* are based on the definitions included in the VARC-2 consensus.[3] For consistency and comparability with other studies, the traditional definition of procedural mortality should refer to the periods between implantation and hospital discharge or between implantation and 30 days follow-up. With respect to the cause of death, all-cause mortality is subdivided into cardiovascular and non-cardiovascular mortality. By conservative approach, sudden or unwitnessed death and any death of unknown cause are classified as cardiovascular death. Left atrial appendage occlusion studies should report on all three categories of mortality, defined in *Table 2*.

Stroke and transient ischaemic attack and peripheral embolism

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction. A transient ischaemic attack (TIA) should be clearly distinguished from ischaemic stroke, based on focal neurological symptoms lasting <24 h and imaging-confirmed absence of acute brain infarction. Therefore, it is mandatory to recommend imaging confirmation as part of the diagnosis of TIA. Stroke assessment requires a neuroimaging and neurological examination, preferentially by a neurologist. Although in registry studies such extensive diagnostics may not be feasible, strokes should minimally be adjudicated by a neurologist based on written information.

An overview of diagnostic criteria for stroke and TIA is provided in *Table 3*.

Infarction of the central nervous system (CNS) is defined as cerebral, spinal cord, or retinal cell death attributable to ischaemia, based on the following:

- Pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischaemic injury in a defined vascular distribution, or;
- Neuroimaging [computed tomography (CT) or magnetic resonance imaging (MRI)] evidence of cerebral, spinal cord, or retinal focal ischaemic injury, or;
- Clinical evidence of cerebral, spinal cord, or retinal focal ischaemic injury based on acute onset symptoms persisting ≥24 h, imaging excluding brain haemorrhage, and other aetiologies excluded.

Strokes should be classified according to the definitions provided by the Clinical Data Interchange Standards Consortium,[31] as listed in *Table 4*.

Cognitive function assessment

Assessment of cognitive function should be considered before, shortly after, and during long-term follow-up of patients undergoing LAAO procedures.

Systemic embolism

Although trials on VKA and NOAC therapies[32–35] as well as on LAAO[14,19,21,23,36] have applied systemic embolism as a primary endpoint for effectiveness, definitions have been variable and inconsistent.

The definition provided in *Table 5* is composed from definitions applied by several trials on VKA and NOAC therapies and is

Table 3 Diagnostic criteria for stroke and TIA[3,31]

Identification of neurological deficit	An acute episode of a focal or global neurological deficit with at least one of the following: • Change in the level of consciousness, • Hemiplegia, • Hemiparesis, • One-sided numbness or sensory loss, • Dysphasia or aphasia, • Hemianopia, • Amaurosis fugax, • Any other neurological signs or symptoms consistent with stroke.
Absence of nonvascular aetiology	No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacologic influences) to be determined by or in conjunction with the designated neurologist.
Stroke vs. TIA	Stroke is defined by an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction. The event classifies as a stroke rather than a TIA based on any of the following: • Duration of neurological dysfunction >24 h, • Duration of neurological dysfunction <24 h in case of imaging-documented new haemorrhage or infarction, • A neurological dysfunction resulting in death. A TIA is defined by any neurological dysfunction not satisfying the above criteria for stroke, specifically if lasting <24 h without imaging-documented acute brain infarction.
Confirmation	For a confirmed diagnosis, these elements (i.e. identification of a neurological dysfunction, absence of a nonvascular mechanism, and differentiation between stroke and TIA) should be supported by both • Assessment by neurologist or neurosurgical specialist, • Neuroimaging procedure (CT scan or brain MRI) findings.

TIA, transient ischaemic attack; CT, computed tomography; MRI, magnetic resonance imaging.

Table 4 Stroke classifications[31]

Stroke types:	• Ischaemic: An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of CNS tissue. Haemorrhage may be a consequence of ischaemic stroke. In this situation, the stroke is an ischaemic stroke with haemorrhagic transformation and not a haemorrhagic stroke. • Haemorrhagic: An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage. • Undetermined An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction but with insufficient information to allow categorization as an ischaemic or haemorrhagic stroke.
Stroke severity	• Disabling stroke: At 90 days after the index event, an mRS score of ≥3 and an mRS score increase of at least 1 compared with pre-stroke baseline. • Non-disabling stroke: Any stroke not satisfying the criteria for disabling stroke (i.e. an mRS score of <2 at 90 days or an increase in mRS score of <1 compared with pre-stroke baseline).
Fatality	• Death from any cause ≤30 days after onset of stroke. • Death due to stroke >30 days after onset of stroke.

mRS score, modified Rankin Scale score. To be assessed by assessed by qualified individuals according to a certification process (not by definition neurologists). In patients in whom a stroke is suspected, examination by a neurologist is optimal.

Table 5 Definition of systemic embolism[32–35]

Systemic embolism	Acute vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g. trauma, atherosclerosis, or instrumentation). When there is presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion.

CNS, central nervous system.

proposed for all patients enrolled in device- or drug-arms of LAAO studies.

Additional details with regard to thromboembolic events

To better understand the aetiology of stroke and systemic embolism, studies on LAAO should document and report on all relevant procedural conditions, such as antithrombotic therapy, timing, extent and target ACT of heparinization, the occurrence of air embolism, catheter and/or device exchanges during the procedure, and the duration of the procedure.

In case of stroke or systemic embolism, all studies of any type should require the following to be performed as immediate as possible after the event:

- full neurological examination,
- imaging (CT or MRI of the brain),
- TEE to identify potential embolic sources.

In studies comparing a device therapy with pharmacological treatment the above examinations should be performed in both study arms.

Device-related aspects to be assessed by TEE following an ischaemic event include thrombus on the device and peri-device leaks. Besides event-triggered TEE, regular TEE is recommended in all patients, with and without events, to monitor the device status and the presence of thrombus or leaks and evaluate their clinical significance. Studies should obtain an appropriate baseline neurological assessment to allow comparison with post-event neurological evaluation.

Pericardial effusion/tamponade

Pericardial effusion with or without tamponade is a potentially severe complication of endocavitary cardiac catheterization; classification of their severity within the context of LAAO benefits from a more detailed and consistently applied definition. Therefore, a definition based on the actual treatment is proposed. Acknowledging the fact that in current clinical practice, pericardiocentesis is not considered a critical, high-risk intervention *per se*, the definitions listed in *Table 6* arise.

All patients should have a baseline echocardiogram. Left atrial appendage occlusion studies should report on all pericardial effusions with severity classified according to the definitions in *Table 6* and specify effusions with tamponade as a subgroup. Of note, the qualification of the event as a major complication does not depend on the presence of tamponade.

Table 6 **Definitions for severity and time of occurrence of pericardial effusion**

Clinically non-relevant	• Requiring no intervention • Treated pharmacologically
Clinically relevant	• Treated with therapeutic pericardiocentesis • Treated with surgical intervention • Requiring blood transfusion • Resulting in shock and/or death
LAAO therapy associated with epicardial approach	• Clinically non-relevant (minor): Requiring no intervention, treated pharmacologically or <500 mL of bloody fluid was aspirated and not requiring blood transfusion or surgical intervention • Clinically relevant (major): Aspiration of >500 mL of bloody fluid or an effusion that required blood transfusion or surgical intervention The presence or placement of pericardial catheter/drain at the end of the procedure should not be considered as clinically relevant effusion
Time of occurrence	Intraprocedural—occurred during the index procedure Acute—up to 48 h from the index procedure Late—more than 48 h from the index procedure

Table 7 **Bleeding definitions**

Life threatening or disabling	• Fatal bleeding (BARC Type 5) OR • Symptomatic bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or intramuscular with compartment syndrome (BARC Type 3b and 3c) OR • Symptomatic pericardial bleeding (with or without tamponade) occurring after hospital discharge for the index procedure OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC Type 3b) OR • Overt source of bleeding with drop in haemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units (BARC Type 3b)
Major bleeding (BARC Type 3a)	• Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dL or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery OR • Pericardial bleeding (with or without tamponade) occurring during the index procedure or during hospitalization for the index procedure • Bleeding causing discontinuation of antithrombotic therapy for stroke prevention, including antiplatelets, VKA and NOAC AND • Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding (BARC Type 2)	Any bleeding worthy of clinical mention (e.g. access site haematoma) that does not qualify as life threatening, disabling, or major

BARC, Bleeding Academic Research Consortium; VKA, vitamin K antagonist; NOAC, non-VKA oral anticoagulant.

Bleeding

In the currently most comprehensive definitions of bleeding associated with cardiovascular interventions, the Bleeding Academic Research Consortium (BARC)[37] includes six severity categories (Types 0–5). In an update of their endpoint definitions for transcatheter aortic valve implantation,[3] the VARC decided to maintain the original severity categories of life-threatening, major, and minor bleeding.[2] The definitions for bleeding in an LAAO context, provided in *Table 7*, primarily follow the VARC-2 definitions,[3] with some LAAO-specific modifications and refinements, and cross-reference to the types of bleeding defined by the BARC (i.e. in contrast to VARC-2, BARC 3a is never considered minor bleeding).

Pericardial bleeding is the most common complication of LAAO. When pericardial bleeding occurs during the index procedure or before hospital discharge for the index procedure and is treated with therapeutic pericardiocentesis without sequelae, it is not considered life threatening or disabling bleeding but only major bleeding. However, symptomatic pericardial bleeding after hospital discharge (with or without clinical tamponade) is considered life threatening. Pericardial effusion, including haemorrhagic effusion, should be classified as a device-specific complication according to *Table 6*. Consistent with the consensus published by the International Society on Thrombosis and Hemostasis,[38] asymptomatic bleeding is not considered life threatening, even if it occurs in a critical organ. As a result, asymptomatic pericardial bleeding as an incidental finding from imaging is not classified as life threatening. By its impact on stroke prevention in high-risk patients, bleeding that leads to a physician's decision to discontinue pharmacological stroke prophylaxis should be considered a major event. The definitions in *Table 7* are adequate for all types of occlusion devices (endocardial and epicardial) and can also be applied to subgroups receiving pharmacological therapy.

Table 8 Definitions with respect to pericarditis

Pericarditis	Inflammatory process involving the pericardium associated with chest pain, pericardial friction rub, and electrocardiogram changes.
Severe	Pericarditis requiring prolonged (>4 weeks) anti-inflammatory therapy, associated with recurrent effusions, or requiring surgical intervention (i.e. constrictive pericarditis).
Non-severe	Other pericarditis.
Early	Occurring within 2 weeks from the index procedure.
Late	Occurring >2 weeks from the index procedure.

Table 9 Definition of vascular access-related complications

Any of the following events with onset ≤7 days after the procedure:

- Haematoma at access site >6 cm
- Retroperitoneal haematoma,
- Arteriovenous fistula
- Arterial complications[a] (thrombosis and/or stenosis and/or distal embolization with clinical ischaemia, perforation, dissection, aneurysm, pseudoaneurysm)
- Venous complications (venous dissection, laceration, perforation)
- Symptomatic peripheral ischaemia/nerve injury with clinical symptoms lasting >24 h
- Vascular surgical repair at catheter access sites
- Pulmonary embolism
- Ipsilateral deep vein thrombosis
- Access site-related infection requiring intravenous antibiotics or extended hospitalization

[a]Arterial access is optional for this procedure.

Pericarditis

Pericarditis may occur as a result of a cardiac intervention, particularly when using an epicardial approach. *Table 8* provides definitions with respect to pericarditis that should be applied in comparative studies on LAAO and other LAA-targeted therapies.

Myocardial infarction

Endoluminal occlusion of the LAA usually does not cause tissue necrosis of the LAA. In contrast, epicardial closure, either device based or surgical, may result in myocardial necrosis. This should be differentiated from necrosis due to a myocardial infarction. Epicardial closure-related necrosis may cause enzyme elevation but does not result in ischaemia, typical ECG changes, and regional wall motion abnormalities. Elevated cardiac enzymes and abnormal ECG related to the necrosis of the LAA after the epicardial technique should not be considered as MI in the absence of an acute coronary cause. Overall, the standard definitions of MI[3,39] should be used for cohort studies on LAAO as well as trials comparing LAAO with other options for stroke prevention.

Access-related complications

Complications associated with obtaining vascular access are an important category of procedural complications of LAAO device implantation. A definition of these complications should include all adverse events that are directly or indirectly related to any of the vascular access sites (venous and arterial), used during the procedure. The events listed in *Table 9* are considered vascular access-related complications. Of note, some of these events also qualify as bleeding and should be reported in both categories. Although for some of the events in *Table 9* other causes cannot be excluded, their occurrence within 7 days after the procedure most likely qualifies them as access related. Additional definitions for access-related complications associated with epicardial and/or minimally invasive surgical approaches are provided in *Table 10*.

Any of the events listed in *Tables 9* and *10* that occur >7 days post-procedure are not considered access related. Consistent with the VARC-2 consensus,[3] vascular complications that are not related to the access site should be reported separately as non-access-related vascular complications. These may include events within and outside of the 7-day procedural window.

Renal and hepatic injuries

The use of contrast medium for angiography and/or cardiac CT prior to or during an interventional procedure may constitute a renal or hepatic burden. In this context, it should be emphasized that severe renal or hepatic insufficiency is a contraindication for VKA or NOAC and consequently may be a reason to consider device-based LAAO. For classification of acute kidney injury, the definitions of the Acute Kidney Injury Network (AKIN)[40] that are included in the VARC-2 consensus[3] are adopted (see *Table 11*).

For classification of hepatic failure, the alert levels defined for the randomized evaluation of long term anticoagulant therapy with dabigatran etexilate trial, comparing dabigatran with warfarin for stroke prevention in AF patients,[41] are considered appropriate (see *Table 12*).

Table 10 Definition of epicardial or minimal invasive surgical access-related complications

Any of the following events with onset ≤7 days after the procedure:
- Perforation of cardiac vessel or cardiac wall requiring blood transfusion or surgical or percutaneous intervention,
- Puncture of pulmonary tissue requiring blood transfusion, chest tube, or surgical or percutaneous intervention,
- Puncture of abdominal organs requiring blood transfusion or surgical intervention,
- Perforation or laceration of superficial epigastric artery or LIMA requiring surgical or percutaneous intervention.

Table 11 Staging system for acute renal injury[3,40]

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine to 150–200% (1.5–1.99× increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 μmol/L)	Less than 0.5 mL/kg/h for more than 6 but <12 h
2	Increase in serum creatinine to 200–300% (2.0–2.99× increase compared with baseline)	Less than 0.5 ml/kg/h for more than 12 but <24 h
3	Increase in renal creatinine to ≥300% (>3× increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 μmol/L) with an acute increase of at least 0.5 mg/dL (44 μmol/L)	Less than 0.3 mL/kg/h for 24 h OR anuria for 12 h

Increase in creatinine must occur within 48 h.
Patients requiring renal replacement are considered to meet Stage 3 criteria, irrespective of other criteria.

Table 12 Definitions for severity of hepatic failure

Mild	sGPT/ALT, sGOT/AST, or Alk Phos >2× upper limit of normal
Moderate	sGPT/ALT or sGOT/AST greater than 3× normal, or bilirubin >2× upper limit of normal
Severe	sGPT/ALT or sGOT/AST >5× upper limit of normal or sGPT/ALT or sGOT/AST >3× upper limit of normal associated with total bilirubin >2× upper limit of normal or development of signs and symptoms of hepatic disease

sGPT, serum glutamic–pyruvic transaminase; ALT, alanine aminotransferase; sGOT, serum glutamic–oxaloacetic transaminase; AST, aspartate aminotransferase; Alk Phos, alkaline phosphatase.

Table 13 Device-related complications

- Device embolization
  - Major: Device embolization that requires repeated catheterization or surgery or results in damage to surrounding cardiovascular structures.
  - Minor: Device embolization resolved by percutaneous retrieval during the procedure without surgical intervention or damage to surrounding cardiovascular structures.
- Device erosion
- Clinically significant device interference with surrounding structure (circumflex coronary artery, mitral valve, pulmonary artery, pulmonary vein)
- Device thrombus
- Device fracture
- Device infection/endocarditis/pericarditis
- Device perforation/laceration
- Device allergy

Device-related complications

Essentially, all complications that are a result of the presence of the device should be considered device-related complications. *Table 13* specifies the device-related complications relevant to LAAO by endocardial or epicardial devices. Regarding device embolization, surrounding cardiovascular structures include those in the vicinity of the implant location (circumflex coronary artery, mitral valve, pulmonary artery, pulmonary vein) and any cardiovascular structures at the location to which the device migrated. Of note, a residual leak is considered an efficacy issue, rather than a device-related complication.

Left atrial appendage occlusion and residual leaks

Effective LAAO, i.e. elimination of the LAA as a thromboembolic source, is the primary technical objective of an LAAO procedure, irrespective of whether the occlusion is achieved from the endocardium or epicardium. Residual leaks have been observed after surgical LAA exclusion, endocardial LAAO, and epicardial LAA closure. Although incomplete surgical LAA ligation is a common observation, its clinical significance is unclear.[42] It has been hypothesized that the creation of a small communication between the LAA and the LA causes local stagnation of blood flow.[42] This would result in a thrombogenic source with similar risk compared with the initial situation. A similar mechanism would apply to incomplete epicardial LAA closure by minimal invasive techniques.

In the PROTECT-AF study,[21] LAAO was evaluated by TEE at 45 days after implantation and complete closure or a leak represented by a jet <5 mm in diameter was a condition for warfarin discontinuation. The criterion of 5 mm was based on results reported from surgical LAA exclusion, being the only relevant data available when the study was designed. Similarly, the PREVAIL trial[23] considered adequate LAA sealing characterized by a jet <5 mm, while other studies[36,43] defined a jet <3 mm as a mild or small leak. A study on the clinical impact of residual leaks[44] did not find a significant effect of either the existence of a leak or its size on the composite endpoint of all-cause stroke, systemic embolism, and cardiovascular or unexplained death. However, authors emphasized that the low event rate requires a larger sample to draw definite conclusions. Despite the existence of residual leaks in the PROTECT-AF cohort, LAAO was demonstrated to be non-inferior to warfarin[21] and resulted in a statistically significant improved clinical outcome compared with warfarin at long-term follow-up.[25] Residual flow is not an uncommon finding after LAA exclusion, irrespective of the applied approach. As its clinical significance is still poorly understood, any criterion to classify the size of the residual leak appears to be highly arbitrarily. Therefore, the current consensus is to assess this parameter in studies on any type of LAA exclusion following a consistent methodology, outlined in *Table 14*.

Studies should report on the distribution of the size of residual leaks. In addition, relevant clinical endpoints such as ischaemic and all-cause stroke, systemic embolism, and cardiovascular or unexplained death should be stratified with respect to the presence and size of leaks. Until the clinical significance of residual leaks has been clearly revealed, use of the term 'complete closure' seems only justified in case of complete absence of residual flow.

Device, technical, and procedural success

Table 15 provides definitions of device, technical, and procedural success, consistent with most LAAO studies reported so far. Correct device position, as an aspect of device success, is to be assessed as immediately as possible after release of the device from its delivery system and accounting for the manufacturer's recommendations for implantation. This assessment should also address the device

Table 14 Methodology suggested for assessment of residual leaks after LAA exclusion

Imaging modalities	• TEE (echo-Doppler, preferably 3D) and/or • Cardiac CT[a]
Global observations	• Identify uncovered lobes • Describe device implantation (location, orientation, deployment, and/or compression)—endocardial devices only • Location of the observed leak(s)—correlation to device components • Compare position and sealing with previous studies
Measurements	• Use multiple TEE views (0°, 45°, 90°, and 135°) or 3D-TEE • Echo colour Doppler TEE: set Nyquist limit to detect low velocity flow (20–30 cm/s). If leak is present, measure only the mosaic (high-velocity) colour of a communicating flow in multiple projections • Use same settings during implantation and follow-up • Document largest measurement as size of leak and achieved angle of measurement by TEE or CT

TEE, transoesophageal echocardiography; CT, computed tomography.
[a]To avoid radiation, CT is recommended only in patients receiving Cardio-CT for other purposes or if no other technology (e.g. TEE) is available or indicated.

Table 15 Success definitions

Device success	Device deployed and implanted in correct position
Technical success	• Exclusion of the LAA • No device-related complications • No leak >5 mm on colour Doppler TEE
Procedural success	• Technical success • No procedure-related complications, except for uncomplicated (minor) device embolization

stability, for instance verified by applying gentle traction to the device before release.[45]

Antithrombotic therapy post-procedure

Antithrombotic therapy after LAAO varies and may include OACs (VKA or NOAC), antiplatelet drugs (aspirin, clopidogrel, etc.), single or combination, for short term or for life, or no treatment. It depends on the device instructions for use, the patient history, the indication for LAAO, the presence of significant residual leaks, etc. For example, based on the results of the PROTECT-AF trial warfarin is prescribed for 45 days after LAAO with the Watchman device (and until a TEE confirms the absence of significant leak),[21] whereas based on solely empirical data LAAO with Amplatzer devices is followed by dual antiplatelet therapy for 1–3 months.[14] Studies should report data on antithrombotic therapy post-procedure in detail, including the duration of therapy, the doses, and any potential changes at follow-up.

Summary/conclusions

Several studies have shown the safety and efficacy of LAAO for stroke prevention in AF patients who are contraindicated or less suited for long-term OAC. In order to further explore and demonstrate the potential of this therapy, additional clinical evidence is required. This document proposes a consistent approach in the assessment and reporting of clinical results by providing definitions for parameters relevant to studies on LAAO, including comparisons with other devices and with surgical or pharmacological therapies.

It is acknowledged that several definitions included in this consensus document may present physicians and their staff with challenges as to the assessment of associated clinical endpoints, particularly for stroke and TIA. However, adherence to these definitions is strongly encouraged in order to create a consistent base of evidence for development of further recommendations with regard to LAAO within the context of all therapeutic options for the prevention of stroke and embolism in AF patients and to facilitate accurate and concordant scientific studies comparing different approaches to LAAO.

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Participants

The following individuals participated in the consensus meeting that agreed the definitions and were involved in the review of this document:

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Endorsement

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