Stroke is a major global health risk causing mortality and long-term disability. A cardiogenic etiology accounts for one out of every five ischemic strokes and the left atrial appendage (LAA) is considered to be the most important source of cardiac emboli. This thesis attempts to reveal the morphological features of the LAA that might predispose to cardioembolic stroke and to evaluate the impact of background factors on LAA morphology and blood flow in non-stroke patients by utilizing computed tomography.
Left Atrial Appendage

CT-based Classification

in Stroke Patients and Healthy Controls
MIIKA KORHONEN

Left Atrial Appendage

CT-based Classification

in Stroke Patients and Healthy Controls

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Left Atrial Appendage: CT-based Classification in Stroke Patients and Healthy Controls

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**ABSTRACT:**

Stroke is a major health risk causing mortality, long-term disability and economic hardship all around the world. Ischemic stroke is responsible for over 80% of all strokes and cardiogenic etiology accounts for approximately one fifth of these ischemic occurrences. The left atrial appendage (LAA) is considered the source of cardiac emboli in over 90% of cases and thus, there is great interest in this small structure. In the majority of cases, non-valvular atrial fibrillation (AF) is responsible for forming thrombi in the LAA by generating an abnormal blood flow pattern in the milieu of the left atrium (LA). If prolonged, these cardiac arrhythmia are also believed to remodel the LA and its appendage. Various imaging modalities have been utilized in attempts to identify LAA features that possibly elevate the stroke risk; recently mainly in patients with atrial fibrillation have been examined by computed tomography (CT). Despite some inconsistencies, most studies suggest that certain morphological class/classes associate with the risk for cardioembolic events. However, there are only a few studies on the LAA variability among non-AF patients and the possible effect that certain medical conditions can exert on the structure.

The purpose of the current study was to analyze LAA morphology in patients with acute ischemic stroke of suspected cardioembolic origin but without AF, and healthy controls undergoing CT. Study populations were formed of patients enrolled in Kuopio University Hospital between years 2005 and 2015. One of the primary goals was to compare LAA morphologies between stroke patients and controls. Moreover, the effect of demographical factors and various medical conditions were examined in conjunction with LAA features in these patients without acute stroke but without diagnosed AF. As a third goal, by calculating the attenuation ratio of injected contrast agent (CA) concentration from the LAA and ascending aorta, it was possible to estimate the filling of the LAA; thereafter morphological features of the LAA and background factors were related to the obtained attenuation ratios.

In this study, one-lobed and more voluminous LAAs were more prevalent in the stroke population compared to control patients. Regarding the non-stroke population, aging correlated positively with body surface area (BSA)-related LAA length, but had no association with morphological class division. In addition, men possessed more multilobed whereas women had longer BSA-related LAAs; being overweight associated with multilobed LAA morphological classes. Short (< 4cm) and one-lobed LAAs exhibited greater attenuation of the CA concentration, reflecting lower blood flow values in the appendage’s distal lumen. The present study findings may help to clarify the normal morphological nature of the LAA and thus, serve as a reference value for future studies. From a clinical perspective, recognizing short and one-lobed LAAs in CT with a tendency towards decreased blood flow may be of value.

National Library of Medicine Classification: WL 356, WG 201, WG 202, WG 330.5.A5, WN 206
Medical Subject Headings: Cerebral Infarction; Heart Atria; Atrial Appendage; Atrial Fibrillation; Tomography, X-Ray Computed; Risk Factors; Age Factors; Reference Values
TIIVISTELMÄ:


Luokitus: WL 356, WG 201, WG 202, WG 330.5.A5, WN 206
Yleinen Suomalainen asiakirjanasto: sydän, anatomia, morfologia, tietokonemetrografia, aivoinfarkti, eteisväinän, ikä, riskitekijät, viitearvot
In the end, it’s not the years in your life that count. 
It’s the life in your years.

– Abraham Lincoln
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This study was carried out in the Department of Clinical Radiology in Kuopio University Hospital during the years 2013-2017 in collaboration with Heart Center and NeuroCenter of Kuopio University Hospital, and in conjunction with Department of Internal Medicine of Keskisuomi Central Hospital. I am grateful for the privilege of having the opportunity to work with all the professionals in these institutes. I admire your expertise.

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In our beautiful home in Haapaniemi, Kuopio, on 4th of October 2017

Miika Korhonen

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List of the original publications

This dissertation is based on the following original publications:


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# Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AA</td>
<td>ascending aorta</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>AFI</td>
<td>atrial flutter</td>
</tr>
<tr>
<td>AT-II</td>
<td>angiotensin II</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>cCT</td>
<td>cardiac computed tomography</td>
</tr>
<tr>
<td>CCTA</td>
<td>coronary computed tomography angiography</td>
</tr>
<tr>
<td>CTA</td>
<td>computed tomography angiography</td>
</tr>
<tr>
<td>CMR</td>
<td>cardiac magnetic resonance</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ESUS</td>
<td>embolic stroke of unknown source</td>
</tr>
<tr>
<td>HU</td>
<td>Hounsfield unit</td>
</tr>
<tr>
<td>IL-6</td>
<td>interleukin-6</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
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<tr>
<td>LA</td>
<td>left atrium</td>
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<tr>
<td>LAA</td>
<td>left atrial appendage</td>
</tr>
<tr>
<td>LAAEF</td>
<td>left atrial appendage ejection fraction</td>
</tr>
<tr>
<td>LAAFV</td>
<td>left atrial appendage flow velocity</td>
</tr>
<tr>
<td>LSPV</td>
<td>left superior pulmonary vein</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricular</td>
</tr>
<tr>
<td>NOAC</td>
<td>non-vitamin K antagonist oral anticoagulant</td>
</tr>
<tr>
<td>MDCT</td>
<td>multi-detector computed tomography</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>RAA</td>
<td>right atrial appendage</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>SEC</td>
<td>spontaneous echo contrast</td>
</tr>
<tr>
<td>SR</td>
<td>sinus rhythm</td>
</tr>
<tr>
<td>PAF</td>
<td>paroxysmal atrial fibrillation</td>
</tr>
<tr>
<td>PeAF</td>
<td>persistent atrial fibrillation</td>
</tr>
<tr>
<td>PV</td>
<td>pulmonary vein</td>
</tr>
<tr>
<td>PVI</td>
<td>pulmonary vein isolation</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>TEE</td>
<td>transesophageal</td>
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<tr>
<td>echocardiography</td>
<td></td>
</tr>
<tr>
<td>TTE</td>
<td>transthoracic</td>
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<tr>
<td>echocardiography</td>
<td></td>
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<tr>
<td>TTR</td>
<td>time in therapeutic range</td>
</tr>
<tr>
<td>VKA</td>
<td>vitamin K antagonist</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
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</table>
1 Introduction

In 1909, Doctor William Welch was apparently the first to suggest that atrial fibrillation (AF) had caused a cardioembolic stroke due to a thrombus in the left atrial appendage (LAA) (1). Prior to this, Virchow, Aschoff and Welch had pioneered the fundamental mechanics of thrombus formation; principles that still exist today (2-4). However, not until decades later was the LAA established as the main location for thrombus in AF patients, even although it had earlier been considered as a trivial and nonfunctional cardiac structure (5).

Currently, the LAA is recognized as the major site of intracardiac thrombi and consequently the origin of cardiogenic strokes (6). Each year over 25 million people worldwide suffer from either a new or a recurrent stroke; of these, a cardioembolic origin is diagnosed in approximately 5 million cases (7). Although the mortality rate has decreased during recent decades, the prognosis is still dismal as one out of every four patients will die within one year (7,8). In addition to the high mortality rate, stroke can cause a variety of long-term disabilities in the survivors causing productivity loss and significant health care costs; thus, representing a huge economic burden (9,10). Comorbidities have a significant influence on the outcome of ischemic stroke, and AF is known to be one of the predictors of a poor outcome (11).

As stroke is responsible for so many deaths, not surprisingly, the LAA has been called the most lethal attachment in the human body (7,12). This has inspired researchers to explore this small structure in detail, especially in patients with AF (13-15). The advent of LAA closing devices as a therapeutic means of stroke prevention further stimulated this research (16-18). As the LAA has been noted to exist in divergent forms, studies regarding LAA morphology, LAA flow velocity and the possible relation to thrombus formation have expanded considerably (19-21). At first, autopsies and echocardiography were utilized in the study design (22,23). The recent advances in the field of in vivo imaging has provided researchers with high-resolution images of this structure and thus clarified the anatomy and physiology of the heart (24). Despite all these many investigations, research on LAA morphology and its relations to ischemic stroke has still to make an impact on clinically-relevant outcomes.

This thesis evaluates LAA morphology in patients with ischemic stroke but without a diagnosed AF together with control subjects without any history of stroke by utilizing cardiac computed tomography (cCT). The first aim was to study whether LAA morphology would be associated with strongly suspected cardioembolic stroke in patients without a history of AF; and furthermore to evaluate, if an association existed, whether certain morphological types would be more prone to form a thrombus. Second, this thesis attempts to reveal possible relationships between various background factors with LAA morphology in patients without stroke and thereby to produce reference data for future studies. Lastly, the impact of LAA morphology on LAA blood flow was examined by using contrast-enhanced CT analyses in non-stroke patients.
2 Review of the literature

2.1 CARDIOEMBOLIC STROKE

2.1.1 Definition epidemiology and risk factors of stroke
Stroke is an acute loss of focal brain function with clear neurological symptoms without any cause other than a vascular origin (25). It can develop either due to cerebral hemorrhage (10%), subarachnoid hemorrhage (3%) or a lack of essential blood flow in a cerebral artery, i.e. there is an ischemic basis (87%) (7). According to the Finnish National Institute for Health and Welfare’s cardiovascular disease registry, the proportion of ischemic strokes in 2013 was 79% (26). If neurological symptoms for a focal ischemic event last for less than 24 hours, the diagnosis of the event is called a transient ischemic attack (TIA) (26). Not only stroke, but also TIA requires immediate hospital care as the risk for an incipient stroke is highest within hours, but remains elevated even weeks afterwards (27).

In 2013, the global stroke prevalence was 25.7 million. It was the second-leading cause of death globally with over 10 million individuals suffering their first stroke (7). Stroke not only is a killer, it is a major cause of disability and it is responsible for approximately 2-4 percent of all health-care costs (8). In Finland, over 21 000 strokes occurred in 2013, of these over 16 000 had an ischemic etiology (26,27). Although the prevalence of ischemic strokes has remained the same during the 21st century, the number of recurrent strokes has decreased. The mortality rate of strokes has also slightly declined during the past two decades and was about 18% in 2014 during 6 months post-stroke follow-up; with ischemic strokes, the mortality rate was 15% (26,28).

According to a recent study, approximately 75% of strokes are related to behavioural factors, e.g. smoking, low physical activity and poor diet. Other known risk factors are high systolic blood pressure and high body mass index (BMI). (29) Age positively correlates with the risk for stroke, and especially after 40 years, the risk increases steeply (30). However, a trend towards increasing incidence at younger ages has been recognized (31). Females are generally older at the time when they experience a stroke; between 55 and 75 years of age females have a higher lifetime risk for stroke than males (7,32). In addition, stroke risk factors differ between genders as women show higher frequencies of hypertension and AF, but possess less diabetes or smoking histories than in men (32).

2.1.2 Classification of pathogenesis of ischemic stroke
Based on the stroke etiology, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) has divided ischemic strokes into five categories: large-artery atherosclerosis (25%), cardioembolism (20%), small-vessel occlusion (25%), stroke of other determined etiology (25%), and stroke of undetermined etiology (5%) (33,34). In a large European stroke registry, cardioembolic strokes were recognized as the most prevalent etiology (26%) followed by cryptogenic (23%), large-artery atherosclerosis (21%) and small-vessel occlusion (21%) etiology (35). In the Helsinki Young Stroke Registry which includes patients aged less than 50 years, cryptogenic strokes (31%), stroke of other determined etiologies (25%) and cardiogenic strokes (20%) prevailed (30).

Large-artery atherosclerosis is associated with over 50% stenotic or occlusive findings in a major brain artery or branch cortical artery, which both have a high probability of resulting in atherosclerosis. In order to make a proper diagnosis, there should be both clinical and brain imaging findings. (33) Clinical findings contain impairment of the cortical areas (e.g. aphasia, motor impairment or neglect), brain stem (e.g. oculomotor dysfunctions, Horner’s syndrome) or cerebellum (e.g. vertigo, dizziness, double vision or incoordination) (36-38). If
the thrombosis is located in the basilar artery, the ischemia affects the brain stem and/or cerebellum (36). Imaging findings should reveal a lesion of at least 1.5 cm in diameter either in CT or magnetic resonance imaging (MRI).

In cardioembolic strokes, the source of ischemia is an embolus, which originated in the heart and was carried with the systemic blood flow into the intracranial vessel, causing an ischemic blockage (39). About 80% of cardiac emboli are directed to the cerebral arteries with the remaining 20% going to the mesenteric or peripheral arteries (40). Approximately one fifth of cerebral emboli end up in the posterior cerebral circulation; thus anterior circulation defects are more common (41). In fact, cardiogenic embolization is the most common known etiology for obstructing the internal carotid artery or the proximal cerebral artery (42). In order to set the diagnosis, large-artery atherosclerosis etiology should be excluded and there must be at least one potential cardiac source for the embolus. These potential sources were first divided into high-risk (e.g. mechanical prosthetic valve, other than lone atrial fibrillation or LAA thrombus) and medium-risk sources (e.g. mitral valve prolapse, left atrial turbulence i.e. “smoke”, lone atrial fibrillation or atrial flutter) based on their relative propensities to cause cardioembolic stroke (33). Thereafter, an updated, evidence-weighted Stop Stroke Study TOAST (SSS-TOAST) classification criteria have been designed to recognize potential risk sources (Table 1) (43). Apart from these sources, a history of previous stroke/TIA in at least two vascular territories or embolus in systemic blood flow supports the diagnosis. The clinical and imaging findings are identical with large-artery atherosclerosis. If the patient is suffering from high-risk cardiac source and other etiological factors for stroke have been excluded, the stroke will be classified as a possible cardioembolic stroke. (33)

Table 1. Sources for cardioembolic events according to the SSS-TOAST classification (adapted from Ay et al.) (43)

<table>
<thead>
<tr>
<th>High-risk primary sources</th>
<th>Low or uncertain primary risk sources</th>
</tr>
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<tbody>
<tr>
<td>Mechanical or bioprosthetic heart valve</td>
<td>Mitral annulus calcification</td>
</tr>
<tr>
<td>Rheumatoid mitral or aortic valve disease</td>
<td>Left ventricular aneurysm without thrombus</td>
</tr>
<tr>
<td>AF or paroxysmal AF</td>
<td>Atrial septal aneurysm</td>
</tr>
<tr>
<td>Sustained atrial flutter</td>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>Thrombus in the left atrium or in the left ventricle</td>
<td>Isolated left atrial turbulence (“smoke”) without mitral stenosis or AF</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td></td>
</tr>
<tr>
<td>Recent myocardial infarction (within 4 weeks)</td>
<td></td>
</tr>
<tr>
<td>Chronic myocardial infarction with ejection fraction less than 30%</td>
<td></td>
</tr>
<tr>
<td>Symptomatic congestive heart failure with ejection fraction less than 30%</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Nonbacterial thrombotic endocarditis</td>
<td></td>
</tr>
<tr>
<td>Infective endocarditis a</td>
<td></td>
</tr>
<tr>
<td>Papillary fibroelastoma a</td>
<td></td>
</tr>
<tr>
<td>Left atrial myxoma a</td>
<td></td>
</tr>
</tbody>
</table>

* Not predominantly of thrombotic origin
Small-artery occlusion (lacunar infarct) is considered if the patient is experiencing one of the traditional clinical lacunar syndromes: pure motor or sensory stroke, sensorimotor stroke or ataxic hemiparesis including dysarthria (44). CT/MRI image finding should be either normal or have a lesion in brain stem or in the subcortical hemisphere (less than 1.5 cm in diameter). In addition, a history of hypertension or diabetes supports the diagnosis. There are some exclusive criteria; patients should display no potential sources for cardioembolic stroke or over 50% stenosis in large extracranial arteries on the ipsilateral side. (33)

Stroke of other determined etiology comprises rare causes of stroke and this cause should be revealed in a diagnostic study. CT/MRI findings of acute ischemic stroke should be visible but are not determined with any specific size or location. In order to set the diagnosis, cardioembolic or large-artery atherosclerosis etiologies must be excluded. (33) The other determined group can be divided into dissection and other non-dissection causes. Non-dissectional causes contain hypercoagulable states (e.g. inherited thrombophilias) and hematologic disorders (e.g. antiphospholipid antibodies). (33,45)

Stroke of undetermined etiology (cryptogenic stroke) refers to all of the cases where the cause of the stroke cannot be specified with confidence. This is due either because there may be more than one potential cause or because despite evaluations, no potential cause for stroke has been identified. (33) Patients with cryptogenic strokes are usually young and lack the usual stroke risk factors (46). According to a gene expression study, over half of the cryptogenic strokes had a cardioembolic etiology when their blood samples were compared with profiles of known cause (47).

A new term, embolic stroke of undetermined source (ESUS), has been suggested to replace the previous negatively defined entity; it contains the following more pragmatic clinical construct: CT/MRI proven non-lacunar stroke, the absence of at least 50% stenosis in arteries that supply the ischemic area, a major-risk cardioembolic source of embolism is missing and no other specific cause for stroke can be identified (34,48). Despite the young age of ESUS patients, they carry a high risk for recurrent strokes (49). In a recent meta-analysis, ESUS was estimated to account for 1 out of every 6 ischemic strokes; the mean age of these patients was younger (65 yrs) than in those experiencing other ischemic strokes and the recurrent stroke rate was 4.5% per year (50). Although cryptogenic stroke and ESUS may be considered as synonyms, some overlap between the terms has been suggested (Figure 1) (51).
Figure 1. Illustration of the overlap between terms. (1) For example, carotid artery stenosis not detected due to lack of proper evaluation (2) Cardiac source present but not detected (3) e.g. atrial thrombosis without recognized AF (4) e.g. carotid artery stenosis which is not detected despite proper evaluation (5) Clinical and imaging profile findings support the diagnosis without large-artery stenosis (6) Cardiac source present but not detected due to lack of proper evaluation (7) e.g. undiagnosed paroxysmal AF that lasts for only short periods each day. Adapted from Kamel et al. (51)

2.1.3 Pathophysiological mechanisms of cardioembolic stroke

The pathogenesis of thrombi may be explained by the three factors first described by Rudolf Virchow over 150 years ago: abnormality in blood flow (stasis), alterations in vessel walls (endothelial injury) and changes in blood coagulability (hypercoagulability) (52). These factors are tightly related to each other and thus the pathogenetic phenomenon is commonly called as Virchow’s triad (53). An abnormal blood flow in the heart may be due to rheological factors, which cause areas of decreased flow inside the atrium (54). These areas are prone to form spontaneous echo contrast with increased haemostatic activation (55,56). Moreover, changes in the normal blood flow cause endothelial damage, endothelial denudation and remodeling of the wall structure (e.g. myocytic hypertrophy, myocardial infarction (MI) and mononuclear cell infiltrate) especially in patients with AF (56,57).

There are multiple reasons that affect the generation of intracardiac blood clots. The most common reason is AF, which increases the risk for stroke on average by 5-fold depending on the amount of concomitant factors (58-60). This arrhythmia will be discussed in chapter 2.2 in more detail. Other risk factors for cardioembolic stroke are described in Table 2.
Table 2. Possible risk factors for cardioembolic stroke and their effect on forming thrombus according to Virchow’s triad.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Disorganised atrial electrical activity and fast irregular atrial contraction results in abnormal blood flow and inflammatory reaction (56).</td>
</tr>
<tr>
<td>Systolic heart failure</td>
<td>Abnormal blood flow because of low cardiac output, dilated chambers and poor contractility. In addition, dysfunction of heart endothelium, and abnormalities in hemostasis and platelets have been demonstrated. (61)</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
<td>Causes ventricular akinesia/dyskinesia which results in abnormal blood flow and endothelial denudation with consequent platelet activation (62).</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>A common (~25%) congenital feature in the heart where an embryologic passage from right to left atrium still exists and, thus, may serve as a pathway for venous thrombi to enter the major circulation. Patient with PFO may suffer more often from cryptogenic strokes. (51,63-65)</td>
</tr>
<tr>
<td>Prosthetic heart valves</td>
<td>Prosthetic valves (mechanical or bioprosthetic) form a foreign surface in contact with the bloodstream and, therefore, form an elevated risk for thrombus formation. Bioprosthetic valves associate with lower risk for stroke but equal long-term mortality with mechanical valves. (66,67)</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>Endocarditis predisposes to the formation of vegetation (i.e. amorphous mass of platelets, fibrin, microorganisms and inflammatory cells), which may detach as an embolic particle. Risk for stroke is elevated months after endocarditis. (68)</td>
</tr>
<tr>
<td>Other risks</td>
<td>Several other, but more rare, etiologies for cardioembolic strokes exist, e.g. mitral calcification and intracardiac tumors (for example, papillary fibroelastoma, myxoma and metastases). Inflammatory mechanism is also associated with progression of atherosclerosis and plaque rupture. (34,51,69)</td>
</tr>
</tbody>
</table>

About 80% of thromboembolic-related deaths are due to ischemic strokes and 20% of other systemic embolic events (70). Regarding post-MI thrombi, nearly 20% disappear after acute phase without any treatment, but in the majority of cases, there is a clear risk for embolization (71). As a thrombus at some point detaches from the heart by blood flow, it directs to the major circulation and, in most of the cases, to the cerebral arteries (40). Clots formed in the left side of the heart are responsible for most of the emboli in peripheral arteries and viscera, e.g. causing acute abdomen (72,73).
The majority of intracardiac thrombi form in the LAA. In cardioembolic stroke, patients with non-rheumatic AF, a thrombus is located in the LAA in approximately 90% of cases; for rheumatic AF, a thrombus is found in LAA or LA in more than 50% of cases. (6) An enlargement of the LAA together with certain morphological features may predispose the subject to the formation of thrombus and subsequent cardioembolic stroke (21,74). In addition to LA and LAA, thrombi may form in the left ventricle, especially after a MI (75).

Cardioembolic stroke may occur also in a paradoxical nature if the thrombosis is generated on the venous side (76). With the existence of patent foramen ovale (PFO) or, more rarely, pulmonary arteriovenous fistula, the thrombus may be carried into the arterial side, resulting in an ischemic state (77,78). In approximately 1% of PFO patients, an atrial septal aneurysm is found and may serve as a potential locus for thrombus formation (79,80). In addition, a higher interseptal membrane mobility has been related to an elevated stroke risk with PFO patients (81).

2.1.4 Clinical aspects of cardioembolic stroke

From a clinical perspective, cardioembolic strokes present sudden neurological symptoms, which are maximal at onset (< 5 minutes) compared to strokes with the etiology of large-artery or small-artery atherosclerosis (82). A cardiac embolus predominates in the territories of carotid and middle cerebral arteries, but affects typically also the distal branches of the main intracranial arteries and, thus, the cerebral cortical areas (Figure 2) (82-84). This results in signs of cortical symptoms, e.g. aphasia or motorical impairment (33). Compared to atherothrombotic infarctions, altered consciousness has also been recognized as predictive factor for cardioembolic strokes (85). Simultaneous or sequential strokes in different arterial territories or, in a minority of cases, rapid regression of symptoms (spectacular shrinking deficit syndrome) may present an important hint of their cardioembolic origin (Figure 2) (39,42). Moreover, the majority of hemorrhagic infarcts are caused by cardioembolism and hemorrhagic transformation (either petechial or multifocal) occurs in up to 70% of cardioembolic strokes. After embolic blockage, this can lead to a local vascular spasm; the fragmented thrombus together with the release of the spasm predisposes capillaries to reperfusion. (42)
Figure 2. Upper images: MRI scans of a patient suffering from cardioembolic infarctions (white lesions) in different arterial territories. Lower image: CT scan of the brain with multiple cardioembolic infarctions in a single arterial territory and petechial hemorrhagic transformation.

As the treatment of dyslipidemia and hypertension has improved in high-income countries, the atherosclerotic stroke prevalence has declined and thus the relative prevalence of cardioembolic strokes has increased (86). In addition, prolonged electrocardiogram (ECG) monitoring after cryptogenic strokes has associated with better detection of AFs and thereby has influenced the occurrence of cardioembolic strokes (87). Cardioembolic strokes that are associated with AF are nearly twice as fatal as non-AF strokes (88). In addition, they cause greater disability, worse functional outcome and lower
prognosis for hospital discharge (89). For these reasons, it is important to recognize cardioembolic strokes promptly in order that the physician can choose the most appropriate secondary prevention (90). The risk of a secondary stroke is highest at the early stage after the primary stroke, and although it declines on a yearly basis, it is still on average six times greater even years afterwards (91,92). Approximately 70% of recurrent cardioembolic strokes may be preventable with oral anticoagulation therapy in patients with AF (93). Moderate or severe LA enlargement and presence of AF are both associated with increased risk for recurrent strokes with embolic etiology (88,94). According to a previous study, the presence of an enlarged LA does not itself modify the risk for stroke in patients with AF (95). In disagreement with this finding, a recent review suggested incorporating the LA size into the current stroke risk scoring system in patients with AF (96).

2.1.5 Routine diagnostic work-up of a suspected cardioembolic stroke
Based on the medical history, physical examination and neurovascular imaging findings, patients with suspected cardioembolic stroke are routinely monitored for rhythm, tested with heart-specific laboratory markers and scanned with transthoracic echocardiography (TTE). These procedures are typically sufficient to identify the majority of cardioembolic sources (Table 3) (97). If no findings exist (i.e. ESUS), a prolonged rhythm monitoring may be performed or imaging with contrast-enhanced TTE, transesophageal echocardiography (TEE) or cardiac CT/MRI may be considered (98).
Table 3. Diagnostic work-up procedures with suspected cardioembolic stroke (adapted from Yang et al.) (98)

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-lead ECG, telemetry and/or 24-hour Holter monitoring</td>
<td>To recognize persistent/paroxysmal AF, atrial flutter and recent myocardial infarctions.</td>
</tr>
<tr>
<td>TTE</td>
<td>To identify left ventricular thrombus, intracardiac masses, vegetations, valve stenosis/thrombus, PFO, septal aneurysm and hemodynamic abnormalities</td>
</tr>
</tbody>
</table>
| TEE | • To confirm or to evaluate the diagnosis for example with infective endocarditis or prosthetic valve thrombosis if TTE is non-diagnostic  
• To evaluate PFO is passage closure is considered  
• To help clinical decision-making if the TTE finding is non-diagnostic |
| Contrast-enhanced TTE/TEE | To evaluate PFO is passage closure is considered |
| Cardiac CT | • To confirm the presence and size of thrombus in prosthetic valve thrombosis and to evaluate the valve motion  
• To help clinical decision-making if the TTE finding is non-diagnostic |
| Cardiac MRI | To help clinical decision-making if TTE, TEE or cardiac CT finding is non-diagnostic |
| Cinefluoroscopy | To confirm the presence and size of the thrombus in the prosthetic valve thrombosis and to evaluate valve motion |
| Prolonged rhythm monitoring with implantable or wearable devices | To recognize silent AF |

### 2.2 ATRIAL FIBRILLATION

#### 2.2.1 Definition and epidemiology

Atrial fibrillation is a common rhythm disorder (worldwide estimated prevalence is 1-2%) with increased mortality and morbidity. The European Society of Cardiology defines AF as an arrhythmia with the following characteristics: surface ECG shows irregular RR intervals without distinct P waves and the atrial cycle is usually variable with a length less than 200 ms, i.e. over 300 beats per minute (99). In AF, the heart rhythm is no longer controlled by sinus node but by different locations of atria resulting in chaotic atrial contractions with a firing rate of up to 600 per minute (Figure 3). However, the ventricular rate is determined by atrioventricular node, which limits the amount of impulses accessing the ventricles resulting in an irregular rhythm. Typically, this rhythm reaches over 100 beats per minute without the use of antiarrhythmic drugs. (59,100,101)

The overall lifetime risk for the development of AF is substantial (~25%) and without predisposing factors still high (~16%) (102). The prevalence increases with age with a baseline prevalence of 7.2% in patients 65 years and older (103). The incidence of AF is greater in men, but with advancing age, the difference decreases (104). AF is predisposed
by both cardiovascular (e.g. hypertension, MI, valvular heart diseases, coronary artery disease, diabetes mellitus) and non-cardiovascular factors (e.g. infections, chronic obstructive pulmonary disease, obesity, alcohol consumption) (102,105-107). In addition, other atrial arrhythmias, e.g. atrial flutter (AFl) or atrioventricular nodal re-entry tachycardia, can trigger the disorder (108,109). As presented earlier, AF is the most critical risk for developing cardioembolic strokes and this risk clearly increases with age (110). For some unknown reason, the stroke prevalence with AF patients is higher in women (111-113).

![Figure 3](image_url)

Figure 3. Illustration of the electrical activity during cardiac cycle in sinus rhythm and in atrial fibrillation. Adapted from Mayo Clinic’s Patient Care & Health Information (114).

### 2.2.2 Diagnosis of AF

The need for ECG registration is usually triggered by symptoms of dyspnea or palpitations. In cases of persistent or permanent AF, the diagnosis is usually straightforward. Otherwise, the need for 24-hour Holter monitoring or other ambulatory methods may be justifiable. (115) According to recent study in cryptogenic stroke patients, AF detection rate progressively increased during the follow-up and reached 30% prevalence at 36 months. Most of these initial events were asymptomatic. (116)

### 2.2.3 Classification and progression of AF

Thoughout the patient’s history, AF may present various forms (Figure 4). The arrhythmia usually initiates in a paroxysmal form (PAF), which lasts up to 7 days until self-termination. The probability of self-termination for PAF after 48 hours is low and thus it forms a clinically relevant benchmark. PAF is considered to initiate most commonly around pulmonary veins (PVs) with rapid focal activity or local re-entry. With time, the number of PAFs typically increases and ultimately PAF is no longer self-
terminated or has lasted over 7 days. This progressive form is called persistent AF (PeAF) and termination by pharmacological or electric cardioversion is needed. However, the clinical distinction between PAF and PeAF is sometimes difficult. As PeAF continues to evolve, the atrial disease advances causing irreversible structural alterations either due to the arrhythmia itself or by underlying disease(s). Thereby, arrhythmia has reached its final form, permanent AF, which is no longer restorable to a sinus rhythm. Sometimes the term “long-standing persistent AF” is used to describe persistent AF with a duration of over a year. (99,109)

Figure 4. Typical progression of AF and its therapeutically suitable actions. Actions in the top yellow bars protect from serious outcomes, e.g. stroke, whereas the blueish bars indicate actions for symptom relief or AF-related complications in the future. Rate control is used both in symptom relief and to improve the cardiovascular outcome. Red bars present the nature of AF with time and the change of AF driver type. The bottom bar displays the transition of AF typical locations. Adapted from European Society of Cardiology’s Guidelines for the management of AF and Iwasaki et al. (99,109)

The term lone or idiopathic AF is considered if there are no clinical or echocardiographic evidence of cardiovascular or pulmonary disease, but the term lacks clear consistency (117). Apart from the usual AF patients, these patients are typically young and they represent normal life expectancy (118).

2.2.4 Pathophysiology
The pathophysiology of AF is diverse and the precise mechanism attributing the arrhythmia is partly unclear. Thus, several factors are likely to accompany the development of AF: an increase in the haemodynamic loading, structural changes of atria, activation of renin-angiotensin-aldosterone system and activation of atrial trigger points (109,119-121). In
addition, after the initiation of AF, arrhythmia itself causes abnormal function of Ca2+ handling and remodeling of atrial structures, autonomic nerves and electrical conduction in a complex pattern (122).

According to current knowledge, AF involves an interaction between the AF trigger points and abnormal atrial tissue that maintains the arrhythmia (123). Both of the cardiac atria contain features that contribute to the pathogenesis but also PVs are crucial in both initiation and maintenance of the arrhythmia (109,124). In general, the PVs seem to have a dominant role in younger AF patients with normal cardiac function and abnormal atrial tissue in patients with structural heart disease (123). When examined electrophysiologically, the driver of AF can be either ectopic firing or re-entry circuit(s) (100). The usual focus has been on the muscular sleeves of PVs, which are vulnerable for both ectopic and re-entrant activity (124,125). Due to its embryologic origin, the LAA is also recognized as one of the trigger sites of AF (126).

AF and congestive heart failure clearly promote each other; AF predisposes to congestive heart failure, which is also one of the best known AF risk factors (120,127). As AF rhythm generates decreased left ventricular function and dilatation, the pressure overload starts to compromise normal left atrial pressure, resulting in an increase of LA size and electrophysiological remodeling (Figure 5) (127,128). In addition, other co-morbidities e.g. obesity, diabetes and hypertension, have been associated independently as risk factors for AF (129,130).

In some cases of lone AF, familial forms are found; e.g. a mutation in KCNQ1 gene on chromosome 11p15.5 has been reported to be responsible for causing a reduced action potential duration and refractory period in myocytes (131,132). Thereafter, a number of other than familial AF genetic risk factors have recognized proving that the genetic background plays a part in the development of non-familial AF as well (133,134).

![Figure 5](attachment:AF_Heart_Failure.png)

*Figure 5. Vicious pathophysiological cycle between AF and heart failure. Adapted from Anter et al. (127)*
2.2.5 Clinical risk assessment
AF confers an increased risk for stroke independent of the AF form (paroxysmal, persistent, chronic), but there are discordant results about whether PAF produces lower or equal risk for embolic events compared to sustained AF (135-137). Nonetheless, stratifying all AF patients with a prediction tool is crucial for the determination of anticoagulation therapy (90). Currently, the evaluation is committed by calculating the CHA2DS2-VASc (congestive heart failure, hypertension, age ≥ 75 years [2 points], diabetes mellitus, stroke/TIA/thromboembolic event [2 points], vascular disease, age 65-74 years, sex category [point for female sex]) score; this has been shown to be a strong predictor of thromboembolic events (138). A patient is considered a low-risk patient if CHA2DS2-VASc score equals 0 for male and 1 for female, and there is no need for anticoagulation therapy. Otherwise anticoagulation with vitamin K antagonist (VKA, typically warfarin) or non-VKA oral anticoagulants (NOACs) is recommended to be considered if the score is 1 for a male or 2 for a female, and strongly recommended if score is ≥2 for a male or ≥3 for a female, because a significant reduction in thromboembolic risk has been achieved with anticoagulation (90,139,140). The risk for bleeding may be calculated with HAS-BLED (hypertension, abnormal renal and/or liver function, stroke, bleeding tendency, labile INR values [TTR<60%], elderly [age > 65 years], drugs or alcohol excess) score to estimate the potential advantages and disadvantages of anticoagulation, and to evaluate the need for anticoagulation (141).

2.2.6 Treatment aspects
Anticoagulation therapy is the only medical treatment, which has clear prognostic significance for AF patients; however, there are several treatment options to control the symptoms of AF. First, arrhythmia may be terminated with cardioversion if the risk for thromboembolic event is assessed low, i.e. 1) AF has lasted for less than 48 hours, 2) more than 48 hours provided that either effective anticoagulation therapy has lasted for at least three weeks, or 3) finding of thrombus in LAA is excluded with transthoracic echocardiography (TEE) (142-144). In addition to electrical cardioversion, the arrhythmia may be reverted to sinus rhythm pharmacologically e.g. by using flecainide, amiodarone or vernakalant (145).

Since most of the cardioembolic thrombi arise from LAA, both surgical removal of LAA and, more recently, percutaneous LAA occlusion with a variety of devices has been of major interest and with promising results (146-150). However, occlusion carries a risk of complications and therefore it may be considered mainly in patients with a high risk for stroke but who are contraindicated for oral anticoagulation (90). Antithrombotic therapy is still necessary in these patients as thrombi may also gather in other parts of left atrium (59). From the interventional perspective, it is essential to recognize the variability in LAA anatomy and thus different morphological classifications have emerged (151-154). LAA anatomy may also influence the stroke risk and in the future, it may be used for patient selection of LAA occlusion procedures (155,156).

Several antiarrhythmic drugs may be utilized both to maintain sinus rhythm in PAF and persistent AF, and to control ventricular rate of AF. The antiarrhythmic drugs used in AF include β-blockers, non-dihydropyridine calcium channel antagonists, digoxin, droxidone and amiodarone. The drug of choice is dependent on whether there is a concomitant heart disease as well as the patient’s lifestyle and other medication. (99)

Another therapeutic modality used with symptomatic drug-refractory PAF is catheter ablation, which has been proved to improve the quality of life, albeit with potential risk for life-threatening complications (157). The usual procedure is to isolate the PVs; over 50% success in a single operation without antiarrhythmic drug therapy has been accomplished (158). In 5 years’ follow-up, half of the patients remained in sinus rhythm with a single ablation and nearly 80% with multiple ablations (159). Atrioventricular node ablation (irreversible procedure of destructing the His bundle) may be considered if the ventricular
rate is high and AF is resistant to other treatments; however, permanent pacemaker implantation may be required (160).

2.3 LEFT ATRIAL APPENDAGE

2.3.1 Left atrium
Of the four cardiac chambers, the LA is located at the most posterior side and more superior in comparison to the right atrium. Four pulmonary veins normally enter the LA at the posterior wall and bring oxygenated blood to great circulation (Figure 6). The vein of Marshall drains the LA posterior wall and joins the coronary sinus during cardiac development, but finally forms a fibrous strand, the ligament of Marshall (Figure 6). In addition to being a conduit for blood, the LA serves as a contractile chamber during the late cardiac diastole, as a blood reservoir during cardiac systole and a structure that refills itself via a suction mechanism in early systole. The LA begins posteriorly at the veno-atrial junction and ends anteriorly at the atrioventricular junction that is marked by the fibro-fatty tissue plane. (161) It possesses muscular walls of non-uniform thickness (average transmural thickness ~4.5 mm) and a relatively smooth-walled interior (161,162). The LA is at its largest at ventricular end-systole. The recommended normal limiting value for LA area is 20 cm² and for LA indexed volume 34 mL/m²; these are considered as upper limits as measured by TTE in the 4-chamber view (163,164).

2.3.2 Definition, anatomy and function of the left atrial appendage
The LAA is a pouch- or finger-like embryologic remnant derived from the primordial LA and begins to originate during the third week of gestation (126,165,166). It is formed mainly by adsorption of the PVs and their branches, which become incorporated into the LA myocardium (167). At first, LAA is a trabecular remnant but the main smooth-walled cavity develops along the PV outgrowth within the confines of the pericardium (13).

After birth, the LAA is present as a projection of the LA with a well-defined junction at the orifice of the LAA (Figure 6) (15). The orifice is usually oval-shaped and located at the same level with the left superior pulmonary vein (LSPV); located above the LSPV in 22-30% of cases and below LSPV in 12-13% of cases (168,169). Typically, the LAA stretches out between the anterior and lateral walls of the LA with its tip directed anterosuperiorly (15). However, the tip position may vary markedly and the LAA may point posteriorly or medially towards the back of the aorta (165). Unlike the right atrial appendage (RAA), LAA is narrow and has a more concise junction (13). Both appendages are trabeculated having parallel muscle bars (i.e. pectinate muscles) formed in a comb-like appearance; however, the LAA has fewer pectinate muscles (166). The LAA exists in various sizes and shapes, i.e. there are alterations in morphologies, and in its relationship with adjacent structures (Figure 7) (15). According to a cast-based study of autopsied hearts, the LAA measures varied greatly in length (16-51 mm), in volume (0.7-19.2 ml) and in orifice size (minimum diameter range 5-27 mm and maximum diameter range 10-40 mm). Moreover, there are variants in the number of LAA lobes: 2 or 3 lobes seem to be the most prevalent form in patients without cardiac disorders (19,170). In addition, with respect to the main LAA, approximately 15% of population may have an accessory LAA or diverticulum, most of these being present in the right anterosuperior position on the LA (169,171).
Figure 6. Location of the LAA and the surrounding structures. Adapted from Romero et al. and Naksuk et al. (24,172) LAA = Left atrial appendage; LA = Left atrium; LCX = Left circumflex artery; LSPV = Left superior pulmonary vein; LIPV = Left inferior pulmonary vein; LOM = Ligament of Marshall; LV = Left ventricle
Figure 7. LAAs (*) of various sizes, shapes and positions seen on CT scans.

The LAA carries out some endocrinological functions concurrently with the RAA and both atrias (173). The cardiac muscle cells in these structures produce and store polypeptide hormones, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), continuously but the rate of synthesis and release is increased if there are the appropriate mechanical or neuroendochronal stimuli (174). The LAA contains about 30% of natriuretic factor, which is the inactive precursor of ANP (175). Oxytocin, hypoxia and myocyte stretching are known factors to stimulate ANP secretion (176-178), which is followed by enhanced diuresis. Furthermore, the production of BNP is increased by hypoxia, and patients with AF, heart failure and LAA dysfunction have proved to exhibit elevated BNP levels (177,179). LAA occlusion significantly decreases BNP levels, but the clinical impact of this decline is currently unknown (180).

2.3.3 Normal LAA flow cycle
The LAA exhibits a distinct contraction pattern compared to the rest of the LA, which can be observed with TEE using Doppler (181). In patients without cardiac abnormalities and in sinus rhythm (SR), the contraction of the LAA is typically biphasic and heart rate dependent with the flow velocity ranging between 50-83 cm/s (182-184) (Figure 8). The maximum flow velocity is usually measured at the proximal third of the LAA (181). In SR during the cardiac cycle, the LAA changes in size and also the diameter of the LAA orifice varies dynamically (15).

The LAA cycle may be divided into four phases. By the time of late diastole, the LAA and its orifice size are at their largest. In this first phase, LAA contracts at the same time with the LA and is associated temporally with the late diastolic mitral flow (“a-wave”)
(185). This is followed by an early systolic filling phase at the beginning of ventricular contraction (183,186). Next follows the reflective passive outward and inward waves with diminishing amplitudes during systole (187,188). The amplitudes of these waves correlate to the velocity of the preceding LAA contraction wave (188). LAA reaches its minimum size at the end of systole (13,15,189). At the beginning of diastole, early diastolic LAA outflow (“e-wave”) may be recorded following early diastolic mitral flow as a result of ventricular relaxation (183,190). (191,192)

Figure 8. The influence of heart rhythm on the LAA flow pattern and flow velocity. In sinus rhythm, four flow phases are recognized: (1) LAA contraction, “a-wave” (2) LAA filling (3) Systolic reflection waves (4) Early diastolic LAA flow, “e-wave”. In AF, the flow waves are rapid and present higher velocities in diastole than in systole. In atrial flutter, flow velocities are higher and slower compared to AF. Adapted from Agmon et al. and Donal et al. (181,192)

2.3.4 Progression of thrombus in the LAA
LAA represents the ideal milieu for thrombus progression as it is a closed-end structure equipped with pectinate muscles and crevices (13,193). The size of a thrombus varies from few millimeters to 4 centimeters and they continuously form and resolve (13,70). The LA thrombus is thought to begin within three days after initiation of acute AF and therefore prophylactic anticoagulation or TEE evaluation is indicated prior to cardioversion; thrombi are found in approximately of 10% of AFs that have lasted for more than two days (70,194).

Reduced LAA flow velocity
The main culprit behind LAA thrombus is typically AF, which causes chaotic atrial contractions and thereby reduced LAA flow velocities, predisposing to blood stagnation, independently of the assessed stroke risk score (Figure 8) (186,195). Moreover, in AF, the LAA flow is highly variable with a sawtooth pattern or a lack of any identifiable flow waves (Figure 8) (182,196). Two distinct flow patterns have been identified; high flow
profile resembles sinus rhythm with peak filling/emptying waves ≥ 25 cm/s while low flow profile is characterized by no visible LAA contraction, irregular flow and with peak filling/emptying waves < 25 cm/s (184). In the low flow profile, the contractility of the LAA is diminished and is more reminiscent of a static pouch instead of a dynamic structure. LAA velocities are significant predictors of thrombi (55,184). Outflow velocities < 40 cm/s are associated with an increased risk for spontaneous echo contrast (SEC) and velocities < 20 cm/s have been linked with an increased risk for thrombus formation within LAA (182,184,187,197,198). Similarly, LAA flow velocity is negatively correlated with the size of the LAA orifice (199).

AFI exhibits regular LAA contractions, higher emptying velocities than AF and, thus, no increased risk for SEC or thrombus. However in AFI with intermittent AF, the flow velocities are lowered and the risk for SEC and thrombi again higher (198,200). To summarize, LAA flow velocities tend to be highest in SR, intermediate in PAF as well as in AFI and lowest in chronic AF (20,198,201,202). In addition to AF and AFI, increased LA area, the female sex, marked left ventricular (LV) dysfunction (e.g. recent MI) and increased end-diastolic pressure in LV (e.g. in patients with dilated cardiomyopathy) may predispose to thrombus generation, by influencing the LAA flow velocity (15,202,203). Furthermore, aging independently associates with decreased systolic flow velocity, which has proved to be a risk for LAA thrombus formation in patients with SR (202,204,205). Although flow velocities are important factors, the presence of SEC in patients with SR seems to display a greater association with stroke risk than reduced emptying velocity (206).

Endothelial inflammation
In prolonged AF, the arrhythmia contributes to remodeling of the LAA causing dilation, a reduction in pectinate muscles and progression of fibrosis (207,208). In women, these changes seem to be more extensive (209). Atrial fibrosis is independently associated with LAA thrombus and increased LAA volume with increased stroke risk (210-212). Apart from normal LAA, the LAA orifice area scarcely changes during the cardiac cycle in AF due to remodeling (15). The fibrosis in the atrial wall is part of the inflammation process in the LA and LAA, most likely caused by AF. This hypothesis is supported by several studies, in which significant increases in the levels of inflammatory markers plasma fibrinogen, interleukin-6 (IL-6) and D-dimer were detected in patients with AF. (213,214) In histopathological studies, AF caused intracellular fibrosis together with cardiomyocyte hypertrophy and nuclear enlargement (215). High C-reactive protein (CRP) levels associate with SEC independent of decreased LAA flow velocity, evidence that inflammation is a major contributor to the thrombogenesis (216). Moreover, a longer duration of AF associates with higher CRP levels and high sensitivity CRP levels correlate with the risk for ischemic stroke as do high plasma IL-6 levels (217-219). These findings suggest that thrombogenesis involves also endothelial dysfunction, which may be due to AF resulting in increased LAA pressure damaging the epithelial cells. In the case of lone AF, inflammation has been suggested even as the initiator of AF rather than its consequence (220). However, recently the term atrial cardiopathy has been proposed to explain partly the initiation of AF also in other than lone AF patients but also to cause stroke independently of AF. Systemic vascular risk factors and aging have suggested to play a crucial role in causing the atrial cardiopathy. (221)

Increasing evidence also indicates that renin-angiotensin-aldosterone system (RAAS) may be responsible for the initiation of the inflammation process due to AF (Figure 9) (121,222,223). Angiotensin-converting enzyme (ACE) converts angiotensin I into angiotensin II (AT-II), which possesses several pro-inflammatory properties by stimulating the production of pro-inflammatory cytokines, adhesion molecules, chemoattractant protein and selectins (224-230). As well as being present in the systemic circulation, angiotensin II receptors are located in cardiomyocytes as human atrial tissue locally expresses ACE. These receptors are upregulated in LA by the stretch influence of AF,
causing an increased inflammatory state and remodeling. (231-234) Moreover, AF seems to increase extracellular signal-regulated kinases, which may contribute to the development of atrial fibrosis (235). The inhibition of RAAS with AT-II receptor blockers or with ACE inhibitors has been shown to prevent the formation of atrial fibrosis, i.e. it has preventive value against recurrent AFs and may decrease the risk for new-onset AF in patients with high risk for AF (e.g. heart failure) (236-240). However with respect to stroke prevention, no evidence has been found that the ACE inhibitors or AT-II blockers offer any benefits over the calcium antagonists (241).

![Diagram](image)

*Figure 9.* The effects of Angiotensin-II on circulation and pathophysiology of left atrium. Adapted from Ehrlich et al. (242)

**Hypercoagulable state**

As a postoperative predictor of AF, von Willebrand factor (vWF) was found to be expressed in LAA tissue, which indicates that there had been endothelial damage or dysfunction prior to the operation and a hypercoagulable state (243). Furthermore, the existence of thrombus or dense SEC correlates with elevated levels of CRP, soluble P-selectin, vWF, D-dimer and hematocrit in patients with AF (55,244,245).

Regardless of the cause, the risk for thrombi relates to impaired LAA function with its reduced contraction and increased filling pressure (15). The reduced contractility of the LAA results in decreased blood outflow and, therefore, increased risk for thrombi (15). The influence of certain morphological characteristics of the LAA regarding thrombus formation will be discussed further in chapter 2.5.4.
2.3.5 LAA embolus
Although thrombi are quite common per se, they do not always form emboli but resolve by themselves as time passes (13,71,246). Risk for embolization is the highest with thrombi that are mobile, prominent and large in size. In addition, age positively correlates with the increased risk. (71) In parallel, a higher risk for stroke in AF patients has been associated with aging (5 times greater in patients of 80-89 years vs. 50-59 years) and female sex (58,111,112,117), but this may also be a consequence of the greater incidence of thrombi. The contrast agent attenuation ratio of LAA/LA in CT seems to be lower in patients with an embolus compared to patients with only a thrombus; the cutoff value of 0.39 yielded a sensitivity of 90% and a specificity of 71% (247).

2.4 IMAGING OF THE LEFT ATRIAL APPENDAGE

2.4.1 Clinical value and indications of LAA imaging
Clinical interest in LAA imaging has increased significantly after its recognition as a major source of embolus (Table 4). Currently, the most typical indications for imaging are exclusion of thrombus prior to cardioversion (in cases where AF has lasted over 48 hours without anticoagulation) and LAA occlusion device implantation (248,249) Moreover, LAA assessment for the existence of thrombus prior to pulmonary vein isolation (PVI) or after cryptogenic/cardioembolic strokes/TIAs have become a part of the clinical routine (250-253). In addition to LAA imaging, excluding other locations and etiologies for the embolus is convenient and necessary with cardiac imaging. Thrombi can be generated in the LA, LV or cardiac valves, and may be due to LV dysfunction, recent MI, cardiomyopathies, prosthetic materials, infections, tumors, aneurysms or in a paradoxical manner from venous side (254).
Table 4. LAA imaging modalities and their properties

<table>
<thead>
<tr>
<th>Modality</th>
<th>Technical improvements</th>
<th>Contrast agent</th>
<th>Typical indication</th>
<th>Advantage</th>
<th>Disadvantages</th>
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<td>Echocardiography</td>
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<td>Ultrasound contrast agent (micro-bubbles)</td>
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2.4.2 Echocardiography

TTE is a noninvasive, “at bedside” modality that usually provides an initial evaluation of the structure and function of the heart. However, the TTE image quality of LAA is usually insufficient for all diagnostic assessments (255). TEE, as an alternative, offers superior visualization of the LAA, because of close distance between esophagus and posterior cardiac structures the signal is not blocked by the lungs or bone (256). Thus, TEE can be sensitive for detecting the source of an embolus, endocarditis or assessing valves or pathological aortic conditions (257). Because of its semi-invasive nature, dysphagia or esophageal operations and bleeding, for example, form contraindications for the procedure (258). TEE is also considered time consuming and may require patient sedation (259).

The development of TEE technology has advanced from monoplane and biplane to multiplane TEE that allows a continuous visualization of cardiac anatomy (260). The use of color flow Doppler helps to evaluate decreased blood flow in the LAA and the pulsed-Doppler further enables the assessment of flow signals and measurement of flow velocities (256). Other enhancements of LAA evaluation include tissue Doppler and strain imaging (261). The former improves the evaluation of LAA myocardial regional function by providing three distinct waves while the latter allows a non-invasive quantification of regional LAA tissue velocities (261,262). The use of ultrasound contrast agent containing microbubbles has been claimed to improve the quality by decreasing imaging artifacts and
thus aid in diagnosis (263-265). Three-dimensional (3D) echocardiography enhances the evaluation of complex LAA geometry in both TTE and TEE compared to two dimensional (2D) echocardiography modalities, and 3D-TEE makes it possible to define the dimensions of the LAA orifice and LAA volumes (266-268). Lastly, during invasive procedures requiring venous access, a catheter-based intracardiac echocardiography may be adapted (269-271).

With regard to its ability to detect LA/LAA thrombus, TEE is currently considered the gold standard due to its excellent sensitivity and specificity, especially with contrast enhancement (Figure 10) (272-276). In visual inspection, a smoke-like, swirling pattern depicts a potential SEC, whereas a thrombus is visualized as a circumscribed mobile or immobile mass (256). However, the interobserver variability has been suggested to be high in the differentiation between thrombus and SEC/reverberation artifacts (259). Thus, routine TEE screening for potential cardiac source of embolism has been criticized, especially in elderly patients (277). In certain situations, the recognition of thrombi with TEE seems to coexist with clinical risk factors, making the procedure unnecessary (278). Furthermore, the combination of 2D and 3D techniques or the use of harmonic imaging with intravenous contrast in TTE has achieved comparable accuracy with TEE (267,279).

Figure 10. Thrombus found in LAA on TEE.

2.4.3 CT
Cardiac CT (cCT) provides a detailed anatomical and physiological assessment of the LAA and its surroundings in a non-invasive manner (280). An accurate understanding of LAA anatomy and orifice dimensions is crucial especially for a successful implantation of LAA occlusion devices (18,281). Whereas the earlier generations of conventional and helical CT scanners were slow and impractical for cardiac imaging, the multidetector CT (MDCT) scanners contain detector elements in a two-dimensional array and allow the acquisition of multiple slices during a single tube rotation. Therefore, the acquisition speed has increased significantly and thinner slice widths together with more coverage of the patient can now be obtained (282). The amount of detector rows in MDCT correlates with the scanner performance, and as the number of rows is multiplied and collimation becomes thinner, isotropic resolution is attained (283). More importantly, MDCT acquires volume data instead of slice data in the helical scan resolution, thus allowing 3D reconstructions; a breakthrough in CT technology i.e. it is now possible to obtain multiplanar reconstructions in coronal, sagittal or oblique planes and high quality volume rendered 3D images (Figure 11) (284,285).
Paralleling the rapid development of scanners, various dose-saving strategies have been implemented as MDCTs have become an increasing source of radiation exposure (286-290). According to the ALARA (“as low as reasonably achievable”) principle, the amount of radiation may be reduced by CT dose optimization technology e.g. by using automated tube current modulation, proper slice thickness and an ECG gating method, and various methods of iterative image reconstruction (288, 289, 291). Obviously, these procedures should not hinder the diagnostic value of CT by excessively reducing the image quality (287). With the introduction of dual-source CT (DSCT) scanners, the radiation dose has declined without any loss of quality (292, 293). As an example of coronary CT angiography, in the (CCTA) study of Khan et al., 64-row MDCT median radiation dose was 6.2 mSv compared to 4.4 mSv dose with a 320-row MDCT (294). A meta-analysis reviewing DSCT radiation exposure revealed that a median value of 2.6 mSv had been achieved (295).

ECG-gating techniques can reduce motion artefacts due to cardiac motion. Two approaches, prospective ECG triggering or retrospective ECG gating, are typically used. In prospective gating, X-ray signals are generated only during cardiac diastole, i.e. the phase when the least cardiac movement occurs. However, this technique is sensitive to changes in the heart rate and it performs poorly if there are arrhythmias. In retrospective gating, ECG is simultaneously recorded with partially overlapping MDCT projections and algorithms (usually either partial scanning or segmented adapted scanning algorithm) to reconstruct the final image using a temporal window. One disadvantage is that it exceeds prospective gating in terms of the radiation dose. (296, 297)

Iodinated contrast medium is usually administered intravenously before scanning the heart. Choosing the optimal timing of image acquisition after the contrast material injection improves the image quality and reveals the coronary arteries. Therefore, CT angiography (CTA or MDCTA) is typically used to rule out coronary artery disease (CAD) with low or intermediate risk patients (298, 299). Concurrently, the LAA is opacified reflecting the bloodstream (300). Pre-procedural imaging has substantial value in clinical routines, for
example, in identifying pulmonary anatomy or measurement of LA and PV ostium prior to AF catheter ablation (301).

CT is a well-established technique, but had been rarely used until recent years for evaluating intracardiac thrombi (Figure 12) (302,303). Thrombi are identified by the reduced or lack of contrast material filling of LAA in CT (281). Meta-analyses regarding the usefulness of cCT for detecting thrombi prior to PV isolation (PVI) procedure or cardioembolic stroke have revealed that cCT is a reliable alternative to TEE, especially when performed with delayed imaging (299,304,305). Due to its sensitivity of 100%, cCT enables confident exclusion of thrombus and obviates the need for TEE (193,306,307). However, filling defects do not always occur in parallel with the presence of a thrombus (i.e. a pseudothrombus resembling slow blood flow in the LAA) and by applying delayed acquisition, the false positivity risk can be reduced also in a low-dose scan (299,308-311). In addition, the visual assessment was claimed to be insufficient for differentiating a thrombus from a SEC (312). Thus as a quantitative evaluation method, Kim et al. presented a protocol for measuring Hounsfield units (HU) within the LAA and relating the value with a reference point, the ascending aorta (AA); a significant correlation was found between LAA/AA HU ratio with an increasing probability of SEC or thrombus (313). Thereafter, attenuation ratio of LAA/AA exhibited also the correlation with LAA velocity in TEE (247). The method has been widely used in previous studies (Table 5), and in the meta-analysis by Romero et al. reached mean sensitivity and specificity of 96% and 92% (299,314). However, Homsi et al. presented that HU ratio analysis did not improve the accuracy over a visual assessment (315).

Figure 12. Examples of thrombi of different size found in LAA on CT.
Table 5. Examples in the published literature regarding the use of LAA/AA HU ratio method with suggested cut-off values for clinical implication assessment.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Modality</th>
<th>N, study group (% AF patients)</th>
<th>HU ratio cut-off value</th>
<th>Clinical implication of cut-off value</th>
<th>Sensitivity, specificity for cut-off value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taina et al., 2016 (316)</td>
<td>16-row cCT + TEE</td>
<td>102 (0%)</td>
<td>0.245</td>
<td>Detection of LAA thrombus</td>
<td>100%,100%</td>
</tr>
<tr>
<td>Budoff et al., 2014 (317)</td>
<td>64-row CCTA + TEE</td>
<td>84 (100%)</td>
<td>0.242</td>
<td>Detection of LAA thrombus</td>
<td>84%,88%</td>
</tr>
<tr>
<td>Choi et al., 2013 (318)</td>
<td>Two-phase dual source CT + TEE</td>
<td>106 (100%)</td>
<td>0.5</td>
<td>Detection of LAA thrombus</td>
<td>96%,90%</td>
</tr>
<tr>
<td>Hur et al., 2013 (319)</td>
<td>Dual-enhancement single-phase cCT + TEE</td>
<td>101 (100%)</td>
<td>0.24</td>
<td>Distinguishing LAA thrombus from circulatory stasis</td>
<td>89%,100%</td>
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<tr>
<td>Hur et al., 2012 (320)</td>
<td>64-row MDCT + TEE</td>
<td>32 (100%)</td>
<td>0.19</td>
<td>Distinguishing LAA thrombus from circulatory stasis</td>
<td>82%,67%</td>
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<tr>
<td>Hur et al., 2011 (321)</td>
<td>Dual-source CT + TEE</td>
<td>83 (34%)</td>
<td>0.2</td>
<td>Distinguishing LAA thrombus from circulatory stasis</td>
<td>80%,85%</td>
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<tr>
<td>Kim et al., 2010 (322)</td>
<td>64-row MDCT + TEE</td>
<td>314 (23%)</td>
<td>0.5</td>
<td>Distinguishing LAA thrombus from SEC</td>
<td>100%,100%</td>
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<tr>
<td>Singh et al., 2009 (193)</td>
<td>64-row MDCT + TEE</td>
<td>51 (100%)</td>
<td>0.78</td>
<td>Predictor of thrombus with TEE</td>
<td>100%,87.8%</td>
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<tr>
<td>Patel et al., 2008 (323)</td>
<td>64-row MDCT + TEE</td>
<td>72 (95%)</td>
<td>0.75</td>
<td>Predictor of LAA thrombus or dense non-clearing SEC on TEE</td>
<td>100%,72.2%</td>
</tr>
<tr>
<td>Kim et al., 2007 (313)</td>
<td>16/64-row MDCT + TEE</td>
<td>223 (100%)</td>
<td>0.25</td>
<td>Distinguishing LAA thrombus from SEC</td>
<td>30%,96%</td>
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</table>

2.4.4 Magnetic resonance imaging
Cardiac MRI or cardiac magnetic resonance (CMR) represents a non-invasive, non-radiative modality for evaluating the morphology and function of the LAA and enabling 3D reconstructions (256). Both comprehensive and accurate data combining cardiac anatomy and dynamic assessment of cardiac function are produced (324,325). Compared to TTE/TEE and cCT, CMR also improves the ability to characterize the state of the tissue (326). Therefore, CMR has been considered as the gold standard for cardiac chamber assessment (327). Typical indications for CMR are CAD, assessment of myocardial viability, perfusion in ischemic heart disease, and characterization of non-ischemic cardiomyopathies, tumours, sarcoidosis and congenital heart diseases (324,328). In addition, it has proved useful in stratifying the risk of AF recurrence, guiding AF ablation and monitoring the post-ablation process (329).
As with CT, CMR imaging can be adapted to incorporate a contrast agent, typically gadolinium, to improve the image quality and tissue characterization by shortening the T1 value of blood and enhancing tissues (330,331). In cardiac cine imaging, both the regional and global contractility of the heart are characterized with blood flow visualization (332). Combining blood flow patterns in terms of 3D volume has generated the promising concept of four-dimensional (4D) flow MRI, improving the evaluation of cardiac function even further (333,334). The CMR synchronization with ECG is applied with similar options as in CT, prospective or retrospective gating. Currently, the typical field strength of CMR is 1.5 – 3.0 T (up to 7.0 T) and slice thickness between 2.5 and 10 mm (331,335-337). The main limitations for CMR are length of the procedure, financial issues and restricted availability combined with contraindications: certain prosthetic materials (pacemakers, defibrillators or aneurysm clips), renal insufficiency (and the risk of nephrogenic systemic fibrosis) and claustrophobia (338,339). However, currently also MRI-compatible pacemakers exist (340).

With respect to evaluating existence of LAA thrombus, delayed enhancement CMR with gadolinium seems to offer a comparative alternative without the semi-invasiveness of TEE or the radiation exposure of CT, and has been suggested as a single diagnostic study prior to the PVI procedure (Figure 13) (330,341). Moreover, it possesses an important role in detecting MI and cardiac viability (342). Its value in differentiating a thrombus from cardiac tumors has been noted and a correlation has been established between velocity encoded CMR and TEE on LAA flow parameters (343,344). A case study also suggested that T2 weighted CMR images have the potential to determine the age of a thrombus (345). However, especially small thrombi may be misdiagnosed despite adapted time-delayed enhancement and therefore there is no consensus on the usefulness of CMR as a clinical diagnostic tool (346,347).

Figure 13. Left image: LAA thrombus recognized by CMR. Right image: Suspected thrombus seen in CMR.
2.5 LEFT ATRIAL APPENDAGE MORPHOLOGY

2.5.1 Aspects on LAA morphology
LAA morphology is characterized by the variability in the structure concerning size, shape, number of lobes and amount of trabeculation. Since it is highly vulnerable to thrombus formation, interest has been focused on the anatomic variation and function of the LAA, as previously described (348). Sharma et al. possibly initiated the exploration of LAA in modern medicine by examining over 1842 LAA specimens from a cardiopathological collection dividing the LAAs according to shape, direction of the hook, existence of a terminal crest, the junction with venous atrium and spillage of the pectinate muscles (349). Veinot et al. continued this mission by studying 500 normal human hearts from autopsies over two decades. Subsequently, the morphological evaluation has proceeded with different imaging modalities, normally in patients with AF (24). The introduction of 3D TEE is one of the latest tools utilized in the morphological and volumetric assessment of this tissue (350-352).

2.5.2 Morphology and background factors
Veinot et al. were the first to study comprehensively the LAA features in normal hearts conduct on autopsy specimens. The results indicated that the orifice size of the LAA increases with age; from 0 to 20 years, the progression is steep, thereafter continues moderately in males but ceases in females. A similar progression was noted regarding LAA maximum width and length in women. However, in men, the LAA length steadily decreases after 20 years of age. On average, men have longer LAAs with greater orifices than women, but these differences did not appear to be significant. (19) Sex or age was reported to exert no impact on the number of LAA lobes nor did body size influence the LAA dimensions (19,170).

Supplementing the results of Veinot, an in vivo study by Boucebeci et al. reported that although LAA volume increases with age, at the same time the LAA ejection fraction decreases in both sexes. In addition, men possessed significantly longer, wider and therefore LAAs with greater volumes. However, body surface (BSA) indexed volumes displayed no difference between the genders. This study found no association between sex and orifice size, but confirmed the influence of age and sex on the number of LAA lobes. (170) The discrepancy may be explained by the different evaluation methods (19,170). According to the latest study, the minimum orifice size increases with age, but this is not the case for the maximum orifice size (170). In another study, age correlated positively with maximum LAA orifice size and LA wall thickness (353). This and other studies have confirmed that LA diameter significantly increases with age (327,353-355). This may imply that increased LA blood pressure causes remodeling in the LAA orifice and its inner structure (353). The report of Aurigemma et al. was in some disagreement, in that although gender and weight associated with LA size, this was not the case for age (356).

The effect of overweight has been evaluated; the amount of epicardial adipose tissue has been associated with reduced LAA ejection fraction (LAAEF) and LAA/AA HU ratio, which may be a result of the increased numbers of adipocytes and their remodeling effects, e.g. to induce myocardial fibrosis and evoke hypokinesia (357,358). The amount of epicardial fat correlates with aging, visceral adiposity and the metabolic syndrome rather than with general obesity (359,360). The decreased LAAEF may be explained by the clear correlation between BSA and LAA volume (348). However, the specific mechanism or endpoint relating to morphological changes seems unclear and modifications may partly occur due to obesity-mediated LA enlargement (361).

Apart from demographical factors, various diseases and their concomitant circumstances may be considered as modifiers of the LAA; e.g. AF, aortic/mitral regurgitation, LV hypertrophy, LV diastolic dysfunction or other causes of heart failure may increase the LA pressure (355,362-365). Since it is a projection of the LA, LAA may be
inevitably affected by either physiological or pathophysiological changes in the LA. In support of this hypothesis, LA volume has been correlated with the LAA short and long orifice diameter, LAA length and LAA volume, but it does not seem to associate with the number of LAA lobes or LAA angle (266,348). There also seems to be a positive correlation between short/long axis of the LAA neck and LAA length; this probably reflects the remodeling effect of the LA size. Despite all of the above correlations, interpatient variability in LAA measures is high. (348)

AF is a well-known factor modifying the LAA. A positive correlation exists between AF duration and both LAA length and LAA orifice size (348,366). In patients with chronic AF, dilation and stretching of the structure occur as well as a reduction in the pectinate muscles and endocardial thickening due to aggregation of fibroelastosis. As a result, the luminal surface area expands. (15,367) These changes may be direct effects of AF and/or a result of dilated LA, an acknowledged consequence of AF (367,368). In PAF, patients in sinus rhythm at the time of measurement displayed significantly lower LAA volumes and greater variation in orifice area during the cardiac cycle than those in AF (368). In addition, after successful AF ablation, LAA orifice size and LAA length markedly decreased, the LAA neck became more eccentric, but the orifice shape remained about the same. However, the decrease in the LA size was prolonged when compared to LAA, which may suggest that remodeling of LAA occurs before the corresponding process in the LA. (369) According to one of the studies, morphological changes appeared prior to changes in LAA contractility, which would indicate that mechanical dysfunction of the LAA is a symptom of structural remodeling (368).

In addition to AF, a negative correlation exists between LV ejection fraction and short axis of LAA orifice as well as a positive correlation between LV systolic dimensions and the short axis of LAA orifice (348).

2.5.3 Morphological classifications
Different morphological classifications have been proposed by combining similar morphological features of the LAA, as seen in Table 6. The initial purpose of these classifications was to aid in the preoperative planning and implantation of LAA closure devices (151). Thereafter, morphological classifications have also attempted to indicate certain classes that confer an increased risk for thrombus (21,370,371).

The most widespread and utilized classification was made by Wang et al., who divided LAAs into four subgroups based on their visual appearance in 3D reconstruction images. The ChickenWing morphology possessed an obvious bend in the proximal or middle part of the dominant lobe, or a folding back of the LAA anatomy and it may also display secondary lobes. The other three morphology classes lack this obvious bend. The WindSock morphology has a dominant lobe with sufficient length and it exhibits with number of secondary or tertiary lobes arising from the dominant lobe in the inferior direction. The Cauliflower has a structure with a limited overall length and a complex internal structure. Variations of this morphology exist with the number of significant lobes without one dominant lobe. The Cactus possesses a dominant central lobe with secondary lobes extending superiorly and inferiorly. Variations of this class relate to the location, orientation and number of the secondary lobes. (151) Whereas Wang’s classification model relies purely on a visual assessment, Kimura et al. introduced quantitative measurements to support the evaluation in an attempt to improve objectivity and interobserver variability. The main assessment tools were the LAA length (with 4 cm threshold), number of LAA lobes and the bend angle of the LAA (Figure 14). (372)
Table 6. Morphological classifications of the LAA in the literature.

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Classification Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacomi’s model (280)</td>
<td>Morphology type 1, 2 and 3 (according to LAA tip orientation)</td>
</tr>
<tr>
<td>Modified Lacomi’s model (153)</td>
<td>Horseshoe, Hand-finger, Fan, Wing, Hook, Wedge, Swan (according to LAA tip orientation and external appearance)</td>
</tr>
<tr>
<td>Li’s model (189)</td>
<td>7 maintypes and 6 subtypes (according to LAA external appearance). Type 1a: horseshoe, Type 1b: cocks’ comb, Type 2a: hand finger, Type 2b: fan, Type 2c: wing, Type 2d: mountain like the Chinese character “山”, Type 3: hook, Type 4: wedge, Type 5: swan, Type 6: fork, Type 7: ring.</td>
</tr>
<tr>
<td>Sakr’s model (373)</td>
<td>Triangular, Rounded, Oval, Tubular, Rectangular, Globular, Slit-like, Other (according to LAA external appearance)</td>
</tr>
<tr>
<td>Shi’s model (152)</td>
<td>Tube, Claw, Sphere-like, Tadpole, Willow-leaf, Sword, Duckbill, Irregular (according to LAA external appearance)</td>
</tr>
<tr>
<td>Wang’s model (151)</td>
<td>Cactus, ChickenWing, Cauliflower, WindSock (according to external appearance)</td>
</tr>
<tr>
<td>Quantitative Wang’s model (372)</td>
<td>Cactus, ChickenWing, Cauliflower, WindSock (according to quantitative measurements)</td>
</tr>
</tbody>
</table>
Figure 14. Morphological categories of the LAA, as based on Wang’s classification with Kimura’s quantitative qualifiers. The dashed line at the LAA orifice represents the base line from which quantitative measurements are made. The blue line indicates how LAA length and bend angle are derived. Differences between the ChickenWing (<100-degrees) and WindSock category (>100-degrees) are also based on the angle at the proximal part of the LAA.
2.5.4 Thrombus formation and LAA morphology
At least to a certain extent, the progression of LAA thrombus is a result of changes in the bloodstream since a strong association has been clearly established with decreased LAA flow velocities (55,374-376). Although it has the ability to estimate the overall thromboembolic risk, the CHA2DS2-VASc risk score has claimed not to be of any use in predicting LAA flow velocity (377). Here, the essential question arises about whether the LAA morphological classes or features are crucial in the generation of stasis and, thereby, of blood clotting.

Despite some discordance between the previous studies, LAA morphological class relates with increased stroke risk in the majority of cases (Table 7). Regarding the studies based on Wang’s model, an association was established in 13 out of 18 studies. In the positive studies, non-ChickenWing, and especially Cauliflower, morphology appeared to be the most vulnerable form of LAA predisposing to the formation of a thrombus. A meta-analysis comprising of eight studies came to the same conclusion (21). As a pathophysiological explanation, Lee et al. suggested that the Cauliflower possesses a lower flow velocity than the other morphologies (376). However, the classification has been considered impractical, and the variability of morphological class proportions among studies using Wang’s classification appeared to be high and furthermore, the reproducibility between studies seems inadequate (378,379). The interobserver agreement has been highly variable, in some studies, being as low as 50% (κ=0.346) although in some others, it has ranged from moderate to high (380,381). Despite the proposition for the initiation of anticoagulant therapy in low-risk patients with non-ChickenWing morphology (Figure 15), before there can be more widespread clinical use, the classification will require more consistency in its evaluation (381).

![Figure 15](image)

*Figure 15. Proposition for the clinical value of evaluating LAA morphological class in AF/AFI patients by Romero et al. (382)*
<table>
<thead>
<tr>
<th>Group, year</th>
<th>Evaluation modality</th>
<th>Indication</th>
<th>LAA evaluation or classification</th>
<th>LAA morphology predisposing to stroke/thrombus or LAA flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 2017 (376)</td>
<td>MDCT + TEE</td>
<td>AF, TIA and stroke groups</td>
<td>Wang’s model</td>
<td>Cauliflower</td>
</tr>
<tr>
<td>Kelly et al., 2017 (383)</td>
<td>CCTA</td>
<td>AF ablation</td>
<td>Wang’s model</td>
<td>Different morphologies not associated with thrombus formation</td>
</tr>
<tr>
<td>Chen et al., 2017 (351)</td>
<td>3D TEE</td>
<td>AF</td>
<td>Wang’s model</td>
<td>Cauliflower</td>
</tr>
<tr>
<td>Jeong et al., 2016 (380)</td>
<td>MDCT</td>
<td>AF and non-AF patients</td>
<td>Wang’s model</td>
<td>Different morphologies not associated with thrombus formation</td>
</tr>
<tr>
<td>Lupercio et al., 2016 (21)</td>
<td>meta-analysis¹ (CT, CMR or 3D TEE)</td>
<td>AF</td>
<td>Wang’s model</td>
<td>Non-ChickenWing</td>
</tr>
<tr>
<td>Fukushima et al., 2016 (384)</td>
<td>MDCT + TEE</td>
<td>AF ablation</td>
<td>Wang’s model</td>
<td>ChickenWing possessed the highest LAA flow velocity</td>
</tr>
<tr>
<td>Lee et al., 2015 (375)</td>
<td>MDCT + TEE</td>
<td>AF</td>
<td>Wang’s model</td>
<td>Non-ChickenWing</td>
</tr>
<tr>
<td>Sakr et al., 2015 (373)</td>
<td>TEE</td>
<td>AF</td>
<td>Sakr’s model</td>
<td>Triangular morphology</td>
</tr>
<tr>
<td>Petersen et al., 2015 (352)</td>
<td>3D TEE</td>
<td>AF</td>
<td>Wang’s model</td>
<td>Non-ChickenWing</td>
</tr>
<tr>
<td>Zhao et al., 2015 (371)</td>
<td>DSCT + TEE</td>
<td>AF ablation</td>
<td>Wang’s model</td>
<td>Different morphologies not associated with thrombus formation</td>
</tr>
<tr>
<td>Nedios et al., 2015 (385)</td>
<td>cCT + TEE</td>
<td>AF ablation group+ control group</td>
<td>Wang’s model</td>
<td>Different morphologies not associated with thrombus formation</td>
</tr>
<tr>
<td>Kishima et al., 2015 (374)</td>
<td>cCT + TEE</td>
<td>AF ablation</td>
<td>Wang’s model</td>
<td>Non-ChickenWing exhibited lower flow velocities</td>
</tr>
<tr>
<td>Li et al., 2015 (189)</td>
<td>MDCT</td>
<td>Various indications for CAD</td>
<td>Li’s model</td>
<td>NA</td>
</tr>
<tr>
<td>Kosiuk et al., 2014 (386)</td>
<td>cCT</td>
<td>AF ablation</td>
<td>Wang’s model</td>
<td>ChickenWing (peri-interventional events), Cauliflower (previous events)</td>
</tr>
</tbody>
</table>
### Table 7 continues

<table>
<thead>
<tr>
<th>Group, year</th>
<th>Evaluation modality</th>
<th>Indication</th>
<th>LAA evaluation or classification</th>
<th>LAA morphology predisposing to stroke/thrombus or LAA flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anselmino et al., 2014 (370)</td>
<td>CT/MRI + TEE</td>
<td>AF ablation + SCI</td>
<td>Wang’s model</td>
<td>WindSock and Cauliflower has increased, ChickenWing decreased risk for SCI lesions</td>
</tr>
<tr>
<td>Yamamoto et al., 2014 (387)</td>
<td>3D TEE</td>
<td>AF ablation</td>
<td>Complex vs. non-complex morphology</td>
<td>Complex morphology</td>
</tr>
<tr>
<td>Kong et al., 2014 (388)</td>
<td>MDCT</td>
<td>AF ablation</td>
<td>Wang’s model</td>
<td>Non-ChickenWing</td>
</tr>
<tr>
<td>Kimura et al., 2013 (372)</td>
<td>CT</td>
<td>AF ablation</td>
<td>Quantitative Wang’s model</td>
<td>Cauliflower</td>
</tr>
<tr>
<td>Khurram et al., 2013 (378)</td>
<td>CT</td>
<td>AF ablation</td>
<td>Wang’s model</td>
<td>Different morphologies not associated with stroke</td>
</tr>
<tr>
<td>Makino et al., 2013 (389)</td>
<td>TEE and cCT</td>
<td>AF</td>
<td>Wang’s model</td>
<td>ChickenWing associated with higher LAA flow</td>
</tr>
<tr>
<td>Di Biase et al., 2012 (390)</td>
<td>CT/MRI</td>
<td>AF ablation</td>
<td>Wang’s model</td>
<td>Non-ChickenWing</td>
</tr>
<tr>
<td>Koplay et al., 2012 (153)</td>
<td>MDCT</td>
<td>Various indications for CAD</td>
<td>Modified Lacomis’ model</td>
<td>Different morphologies not associated with thrombus formation</td>
</tr>
<tr>
<td>Shi et al., 2012 (152)</td>
<td>CTA</td>
<td>AF or ASD</td>
<td>Shi’s model</td>
<td>NA</td>
</tr>
<tr>
<td>Wang et al., 2010 (151)</td>
<td>cCT</td>
<td>AF ablation group+ non-AF group</td>
<td>Wang’s model</td>
<td>NA</td>
</tr>
<tr>
<td>Lacomis et al., 2007 (280)</td>
<td>CT</td>
<td>non-AF and AF patients</td>
<td>Lacomis’ model</td>
<td>NA</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; ASD = atrial septal defect; CAD = coronary artery disease; cCT = cardiac CT; CT = computed tomography; CTA = CT angiography; LAA = left atrial appendage; MDCT = multidetector CT; MRI = magnetic resonance imaging; NA = not available; PAF = paroxysmal AF; SCI = silent cerebral ischemia; SD = standard deviation; TEE = transesophageal echocardiogram

1 The analysis included studies from Di Biase, Fukushima, Kimura, Khurram, Kong, Lee, Nedios and Petersen.

In addition to the above morphological classification, specific morphological features have been associated with an increased risk for low LAAFV/elevated thrombus formation and thus for stroke (Table 8). With some exceptions, increased LAA volume has been associated with a risk for thromboembolic events, and Burrell et al. suggested a threshold of 34 cm³ as posing an elevated risk (212,376,383,390). However, according to Fukushima et al. the greatest LAA volumes are associated with ChickenWing and WindSock, which would
Table 8. LAA morphological features that have been claimed to associate with thromboembolic risk in the literature

<table>
<thead>
<tr>
<th>Morphological feature</th>
<th>Pathophysiological explanation</th>
<th>Notices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased LAA volume</td>
<td>Promotes low blood flow and, thereby, stasis. LAA volume has negative correlation with LAA flow velocity.</td>
<td>Increases risk by 12-fold (Jeong et al.). LAA volume &gt; 34 cm³ threshold increases the risk significantly (Burrell et al.).</td>
</tr>
<tr>
<td>Greater LAA length</td>
<td>As with increased volume, promotes low blood flow and, thereby, stasis.</td>
<td></td>
</tr>
<tr>
<td>Larger LAA ostium area/dimensions</td>
<td>Promotes low blood flow and, thereby, stasis. LAA flow velocity correlates negatively with orifice size.</td>
<td>LAA orifice size &gt;3.5 cm² increases incidence of stroke (Lee JM et al.)</td>
</tr>
<tr>
<td>Smaller orifice size</td>
<td>May lead to greater stasis by hindering the LAA blood flow.</td>
<td></td>
</tr>
<tr>
<td>Extensive LAA trabeculation</td>
<td>Potential cause of stasis by affecting the blood flow.</td>
<td>Increases risk by 3-fold</td>
</tr>
<tr>
<td>Number of LAA lobes</td>
<td>Excessive number of LAA lobes decreases LAA emptying velocity and predisposes to stasis.</td>
<td>≥3 lobes increase risk by 9-fold</td>
</tr>
<tr>
<td>Higher LAA orifice position</td>
<td>Orifice position may predispose to lower flow, because of the distance to mitral annulus and concomitant arrhythmia.</td>
<td>Increases stroke risk by 9-fold (Nedios et al.)</td>
</tr>
</tbody>
</table>

A discrepancy also exists about the LAA orifice size; the majority of studies (6/9) suggest that a larger LAA ostium predisposes to lower blood velocity, but one study reported the opposite and others (2/9) described non-significant results (74,199,366,373,374,376,378,380,388). To support the finding of the majority of studies, the LAA emptying index has been positively correlated with changes in the LAA area and diameter (368). However, this debate has not been resolved since there are the divergent results regarding the orifice size and LAA morphological classes; some studies suggest that ChickenWing has the smallest with WindSock having the largest orifice diameter whereas others state that Cactus has the smallest diameter with Cauliflower exhibiting the largest diameter (372,375,376,378,384). However, the different types of LAA ostium shape (oval, foot-like, triangular, water drop-like, round) might have introduced bias into the measurements (151).

An extensive trabeculated morphology, caused by pectinate muscles, was considered a risk factor in a single study; however, as Cauliflower is considered to be the most trabeculated LAA class, this observation would support the hypothesis of increased risk of non-ChickenWing morphologies (378,384). In addition, internal complexity due to the number of LAA lobes has been claimed to be a potential cause of blood stasis by decreasing
LAA emptying velocity, but once more, this claim has not been confirmed by other study results and it would also be at odds with the Cauliflower stroke hypothesis (371,387). From another perspective, the height of LAA takeoff may be likely to reduce the flow velocity into LAA as the distance to mitral annulus increases (371,385).

As seen in Table 7, almost all of the previous studies were conducted on patients with AF. Therefore, as previously described, AF may have remodeled the LAA structure, introducing a potential bias into these assessments.
3 Aims of the study

The LAA represents a crucial source in cardioembolic strokes. The majority of previous studies have concentrated on imaging the LAA in patients with AF. Therefore, this thesis has analyzed LAA morphology in patients with acute ischemic stroke, with a suspected cardiogenic etiology but without a history of AF, and in patients without acute stroke, using a multidetector CT imaging modality.

The specific aims of the study were:

1. To compare LAA morphologies between non-AF patients with ischemic stroke of suspected cardiogenic etiology and controls. To evaluate the feasibility and interobserver reproducibility of LAA morphological classification. (I)

2. To study the influence of various demographical factors and medical conditions on LAA morphology in non-stroke control individuals. (II)

3. To examine LAA flow using contrast agent attenuation method in non-stroke patients undergoing coronary CTA and to compare the values with LAA morphologies and background factors. (III)
4 Materials and methods

4.1 ETHICAL ASPECTS

The Kuopio University Hospital Research Ethics Board approved the study (N:o 82/2004). All clinical investigations were conducted according to the principles of the Declaration of Helsinki. The Chair of the Hospital District waived the need for written informed consent regarding retrospective analyses of CTA patients.

4.2 STUDY POPULATIONS

4.2.1 Stroke/TIA population and control patients [I]
Patients with acute stroke/TIA admitted to Kuopio University Hospital (KUH) between March 2005 and November 2009 were evaluated as candidates for the EmbodeteCT study (392). Altogether 162 consecutive patients who had been evaluated by neurologists and had acute ischemic stroke of cryptogenic or suspected cardiogenic etiology without previously reported AF and without AF diagnosed at the time of enrollment were recruited. Prior to participation in the study, written informed consent was obtained from each patient or their legally authorized representative if a patient was unable to provide consent due to impaired mental or physical function caused by the stroke.

After enrollment, ambulatory 24-h Holter ECG was performed. A total of 51 patients were excluded after recruitment for the following reasons: confirmed small vessel disease or carotid/vertebral artery stenosis (n=38), cCT image quality inappropriate for LAA morphology analysis (n=4), ECG synchronization failed (n=3), contrast media injection failed (n=2) or was contraindicated due to renal insufficiency (n=1), and refusal to participate despite previously giving informed consent (n=3). The remaining 111 patients (74 males; mean age 60.4 ± 11.2 years) formed the main stroke group for the study (Figure 16).

Forty patients (21 males; mean age 53.9 ± 9.3 years) were selected to form a matched stroke subgroup for pairwise comparisons with the healthy controls. In addition, the main stroke group was compared to healthy controls.

Regarding the control patients, a total of 243 consecutive patients underwent coronary CT angiography (CCTA) at KUH for exclusion of CAD between December 2008 and July 2011. After excluding patients with coronary artery stenosis ≥50%, AF, hypertension, renal insufficiency, malignancies, or any neurological diagnosis, including any symptoms indicating stroke or TIA, 124 suitable candidates were available for pairwise comparisons for stroke/TIA patients (Figure 16). No additional 24-h Holter ECG monitoring was performed. Forty individuals (21 males; mean age 53.8±9.0 years) were used to form the control population and to create age- and gender-matched pairs with the matched stroke/TIA population.
4.2.2 CTTA study population [II, III]
The study population comprised consecutive patients admitted to KUH for CTTA between October 2009 and July 2015. The main indications for imaging were to rule out CAD in patients with a low to moderate pretest probability, to screen for heart failure etiology, or to identify coronary anomalies. This study also included young patients undergoing a preoperative evaluation prior to cardiac valve surgery due to mitral or aortic valve regurgitation, but excluding aortic stenosis. Altogether, 816 patients were imaged. Excluded patients included 3 who were less than 18 years of age, 3 because their LAA could not be reliably assessed from the CTTA image, and 2 patients who suffered AF during CTTA. Thus, 808 patients formed the final CTTA study population.

4.3 IMAGING MODALITIES
Imaging protocol adhered to conventional clinical procedures. Imaging was performed in mid-diastole with the entire LAA fully opacified with contrast media. Cardiac imaging was performed during sinus rhythm apart from two excluded AF patients. To achieve a target heart rate of <65 beats per minute, non-stroke/non-TIA subjects with higher initial heart rates were administered 5-20 mg of intravenous metoprolol prior to their examination.

In the stroke/TIA population and its control patients, contrast-enhanced CCT was performed with a 16-slice (113 patients) or 64-slice (36 patients, 40 control patients) scanner (Somatom Sensation 16 and Somatom Definition AS; Siemens Medical Solutions, Forchheim, Germany). In stroke patients, the aortic arch and cervical and intracranial arteries were scanned first, immediately followed by the ascending aorta and heart. In the 16-slice scanner, collimation was 16×0.75 mm, rotation time 0.42 s, and tube potential 120 kV; the current was set to 500 mAs for the first 80 patients and reduced to 250 mAs thereafter. In the 64-slice scanner, collimation was 64×0.6 mm, rotation time 0.33 s, and tube potential 120 kV; the reference current was set using commercially available tube current
modulation software (CAREDose4D, Siemens Medical Solutions). In CCTA, the collimation was 64×0.75 mm, rotation time 0.17 s, tube potential 120 kV, and mean tube current 327 mAs. Mid-diastolic 0.75 to 1.0-mm-thick slices with 20–25% overlap were reconstructed. The radiation dose per patient was 10.0±3.5 mSv in patients with stroke and 7.9±2.3 mSv in patients with CCTA.

In the CCTA study population, imaging was performed with 64-, 128- slice, and dual energy scanners (Somatom Definition AS 64; Somatom Definition AS+ 128; Definition Edge; Definition Flash, Siemens Medical Solutions, Forchheim, Germany) with tube voltages 80-120 mV. Imaging was initiated at the level of the tracheal bifurcation and then terminated inferior to the cardiac apex. Following scout acquisition to ensure the precise timing of contrast injection, a test bolus of 10 ml contrast was administered and measured 5 mm superior to the origin of the left main coronary artery with dual energy scanners; bolus tracking was used for the other scanners. The volume of the contrast agent (Omnipaque 350 mg/ml, GE Healthcare) was 50-80 ml, delivered at an injection rate of 5 ml/s, followed by a 30 mL saline chaser. Collimation was 64×0.6 mm for the Somatom Definition AS 64, and 128×0.6 mm for all other scanners. The kVp level was adjusted according to patient size. Tube current modulation was used in every patient. The in-plane resolution was 512x512 pixels, with the z-axis coverage including the area from the carina to the diaphragm. Prospective ECG gating provided helical scan data. Images were reconstructed immediately after scanning; electrocardiographically gated datasets were routinely reconstructed at the 75% phase in the cardiac cycle and, in case of helical scanning, 200-400 ms after the R wave. The mean effective radiation dose (mSv) during CCTA in the study population was estimated using the conversion factor of 0.028 (393).

### 4.4 DATA ANALYSES

#### 4.4.1 Image analyses

Quantitative image analysis for stroke/TIA patients and their controls was performed on an IDS5 diagnostic workstation (version 10.2P4; Sectra Imtec, Linköping, Sweden) by three independent observers blinded to collateral readings and all aspects of the patients’ histories. Similarly, the images of CCTA study population were retrospectively analyzed by a single observer using an IDS7 diagnostic workstation (version 17.3.6; Sectra Imtec, Linköping, Sweden). A multiplanar reconstruction provided a three-dimensional perspective. After individual assessments among stroke/TIA patients and their controls, a consensus was reached based on the visual and quantitative observations. To assess reproducibility of the classification of LAA morphology, two observers re-evaluated altogether 40 randomly chosen stroke patients from the main stroke group. In these patients, morphologies were analyzed in both arterial and venous phases.

In all populations, LAAs were visually and quantitatively analyzed with respect to the length, number of lobes, and morphological classification. LAA morphology was defined according to the classifications of Wang et al. and Kimura et al. by assigning the LAAs into four classes: Cactus, ChickenWing, WindSock, and Cauliflower (Figure 14) (151,372). LAA length was measured from the center of the orifice to the most distant point of the LAA, via the center of the main lobe. In the first publication, the LAA bend angle was measured between an imaginary perpendicular line and LAA tip. In later publications, bend angle was measured between the axis of the main lobe and the possible secondary lobe (Figure 14). Based on the number of lobes, LAAs were classified as one-, two-, or multi-lobed structures.

In stroke/TIA patients and their controls, the observers defined the following measurements: shortest distance to the LAA orifice from the mitral annulus (in millimeters), amount of intra-LAA trabeculation (mild, moderate, or severe), and orientation of the LAA tip (up, horizontal, down).
With CCTA population, regions of interest of equivalent size and as large as feasible were estimated to measure HU values from the AA and LAA. These were used to derive LAA/AA HU ratios (Figure 17). When testing the LAA/AA HU ratio interobserver reproducibility, a second observer measured the HU values of 97 consecutive patients. Radiologists or cardiologists evaluated the degree of coronary atherosclerosis and measured the size of the LA using the optimized mid-three-chamber projection of CCTA images at the mid-diastolic phase. The degree of coronary stenosis and LAA filling defects (indicating a thrombus) were evaluated visually. Non-calcified arteries displayed no signs of atherosclerosis.
Figure 17. Hounsfield unit (HU) values measured from four patients. Regions of interest are created from the center of the ascending aorta, and from the distal part of the left atrial appendage (LAA). Regions of equal size were derived, taking care to avoid trabeculated LAA areas.
4.4.2 Data analyses
Medical records provided information on patients’ demographic data and diagnosed medical conditions. Overweight patients were classified as having either a BMI of over 25, or they had been mentioned as being overweight in the medical records. Similarly, obese patients had BMI values of over 30. Diabetes was not classified into subtypes. Smokers included those who smoked regularly, or had a history of smoking but had stopped less than 30 years ago. Coronary artery diameter stenosis of over 50% was considered to be hemodynamically significant. The presence and the severity of valvular disease was assessed from the echocardiographic results. Valvular regurgitation was classified as mild, moderate, moderately severe, or severe. The presence of either moderately severe or severe valvular disease was noted as being of hemodynamic significance.

Body surface area (BSA) was calculated using Mosteller’s formula (394). Thereafter, to minimize the influences of body mass and height on LAA length and LA area, relative values were derived by dividing measurements for LAA length and LA area by BSA values.

With regard to the CCTA population, the use of either a test bolus or a bolus tracking method was registered. In subsequent statistical analyses and to distinguish LAAs that might predispose to SEC, the LAA/AA HU ratios were split into two groups, with a cut-off value of 0.75 (323).

In the stroke population, LAA volumes were calculated using Simpson’s method by multiplying each manually traced area by the section thickness and summing the volumes of the separate sections (395). Based on the volume measurements in the control population, the upper threshold for normal body surface area -adjusted (BSA-adjusted) LAA volume was defined as 5.6 mL/m2 (211).

4.4.3 Statistical methods
In the assessments of the relationships between age and LAA morphology, the CCTA study population was subdivided based on median age, age-related quartiles, or the following age categories: <40 years, 40-49 years, 50-59 years, or ≥60 years.

Continuous variables are presented as mean ±SD and categorical variables as absolute values and percentages. Significance was set to P<0.05, with high significance denoted by p<0.001.

Spearman’s correlation coefficient was used to investigate the associations between continuous variables, with the Chi-Square test applied to investigate nominal variables. Based on the outcome of the Kolmogorov-Smirnov test, either the Student’s t-test or Mann Whitney U test, was used to compare dichotomized groups for normally distributed or abnormally distributed variables, respectively. The Kruskal-Wallis test was used to analyze continuous variables between multiple groups, with linear regression analyses used to calculate the effects of background factors on relative LAA length and relative LA area as a dependent continuous variable. Cohen’s kappa was used to test reproducibility of the assessments.

Regarding the data of stroke/TIA population and their controls, Bonferroni correction was used to counteract the problem of multiple comparisons in four LAA morphologies, which set the significance at P<0.0125. An enlarged LAA was defined as LAA volume exceeding the mean volume in the control population by at least two standard deviations (SDs).

Linear regression analysis was used to calculate the effect of various factors on the HU ratio as a dependent continuous variable and with binary logistic regression on HU ratio as a dependent nominal variable. WindSock morphology was selected to represent the constant factor for these analyses. Consequently, R² values were calculated to report the fit with the regression model. The interobserver reproducibility with continuous variables was tested with intra-class correlation coefficient, with two-way mixed effect to produce Cronbach’s alpha values.
With stroke/TIA population and their controls, data were analyzed using SPSS for Windows (version 19, 1989–2010 SPSS Inc., Chicago, USA), and with CCTA population SPSS for Mac (version 22, 1989–2013 SPSS Inc., Chicago, USA).
5 Results

5.1 LAA MORPHOLOGY IN PATIENTS WITH SUSPECTED CARDIOGENIC STROKE WITHOUT A HISTORY OF AF [I]

The clinical characteristics of the patients in the main stroke group, matched stroke subgroup and control group are presented in Table 9. The patients in the matched stroke subgroup were significantly more obese, had larger BSA values, and more hypertension. The interobserver reproducibility in the study was at a good level (κ=0.65).

Table 9. Clinical characteristics of the main stroke group (n=111), the matched stroke subgroup (n=40) and control group (n=40)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Main stroke group (n=111)</th>
<th>Matched stroke subgroup (n=40)</th>
<th>Stroke-free control group (n=40)</th>
<th>P value 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60.4 ± 11.2</td>
<td>53.9 ± 9.3</td>
<td>53.8 ± 9.0 ns</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>74 (66.7)</td>
<td>21 (52.5)</td>
<td>21 (52.5) ns</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.8 ± 4.4</td>
<td>28.7 ± 4.8</td>
<td>25.3 ± 4.1 0.002</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>63 (56.8)</td>
<td>16 (40.0)</td>
<td>0 (0.0) &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>39 (35.1)</td>
<td>14 (35.0)</td>
<td>16 (40.0) ns</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (10.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0) ns</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>27 (24.3)</td>
<td>9 (22.5)</td>
<td>1 (2.5) 0.003</td>
<td></td>
</tr>
<tr>
<td>AF or AFl on 24-hour ambulatory Holter ECG</td>
<td>17 (15.3)</td>
<td>0 (0.0)</td>
<td>0 (0) ns</td>
<td></td>
</tr>
<tr>
<td>Left ventricle ejection fraction, %</td>
<td>63.6 ± 10.4 2</td>
<td>66.0 ± 10.2 3</td>
<td>63.7 ± 7.7 ns</td>
<td></td>
</tr>
</tbody>
</table>

AF = Atrial fibrillation; AFl = Atrial flutter; ECG = electrocardiogram

1 Statistical significance between matched stroke subgroup and stroke-free control group
2 n = 109
3 n = 37

5.1.1 Single-lobed LAAs more frequent in the main stroke group [I]
Single-lobed LAAs were significantly more frequent in the main stroke group (39% vs. 15%; P<0.01), and even more frequent in the matched stroke subgroup (55% vs. 15%; p<0.001), compared to controls. This difference is illustrated in Figure 18.
Figure 18. Prevalence of single-lobed LAA and multiple lobe (≥ 2) LAA in the three study groups.

5.1.2 The distribution of morphology types between the main stroke group and the control group [I]
A significant difference was found between the main stroke group and the control group (p<0.01) regarding the distribution of morphology types. The difference was highly significant (p<0.001) between the age- and gender-matched stroke subgroup and the control group (Figure 19). After Bonferroni correction, ChickenWing morphology was significantly more frequent in the matched stroke subgroup (p=0.008), whereas the proportion of WindSock was decreased (p=0.007) compared to controls.
Figure 19. Prevalence of LAA morphologies among the three study groups.
5.2 LAA MORPHOLOGICAL FEATURES IN CCTA PATIENTS WITHOUT ACUTE CARDIOVASCULAR CONDITIONS [II]

The original study group comprised 808 patients (mean age 52.5 years, 529 women). The majority (n=749) of these patients had no history of AF. Patients with AF were older, more frequently male, and were more likely to have a history of stroke, TIA and significant valvular disease. Detailed population characteristics are presented in Table 10.

5.2.1 Influence of age regarding relative LAA length and LA area
Higher age was associated with longer BSA-related relative LAA lengths (r=0.156; p<0.001), and larger relative LA areas (r=0.861; p<001), but had no influence on LAA morphological class or the number of LAA lobes. Associations with different age groups are presented in Table 11 and illustrated in Figure 20.
Table 10. Clinical characteristics of the CCTA study group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N=808)</th>
<th>Non-AF patients (N=749)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>Analyzed, N</td>
</tr>
<tr>
<td>Age, years</td>
<td>52.5±9.9</td>
<td>808</td>
</tr>
<tr>
<td>Females (%)</td>
<td>529 (65.5)</td>
<td>808</td>
</tr>
<tr>
<td>Overweight</td>
<td>419 (61.4)</td>
<td>682</td>
</tr>
<tr>
<td>Obese (BMI&gt;30)</td>
<td>163 (31.0)</td>
<td>525</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.93±0.25</td>
<td>527</td>
</tr>
<tr>
<td>Hypertension</td>
<td>409 (50.6)</td>
<td>808</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>488 (64.7)</td>
<td>754</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42 (5.7)</td>
<td>740</td>
</tr>
<tr>
<td>Smokers</td>
<td>251 (33.8)</td>
<td>743</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>700 (86.6)</td>
<td>808</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>5 (0.6)</td>
<td>808</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>58 (7.2)</td>
<td>808</td>
</tr>
<tr>
<td>Chronic AF</td>
<td>1 (0.1)</td>
<td>808</td>
</tr>
<tr>
<td>Non-calcified and non-stenotic coronary arteries</td>
<td>450 (55.7)</td>
<td>808</td>
</tr>
<tr>
<td>Over 50% stenosis in coronary arteries</td>
<td>142 (17.6)</td>
<td>808</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>11 (1.4)</td>
<td>808</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>39 (4.8)</td>
<td>806</td>
</tr>
<tr>
<td>Moderately severe or severe mitral regurgitation</td>
<td>6 (0.7)</td>
<td>808</td>
</tr>
<tr>
<td>Moderately severe or severe aortic regurgitation</td>
<td>16 (2.0)</td>
<td>808</td>
</tr>
<tr>
<td>LA area, cm²</td>
<td>18.8±5.7</td>
<td>204</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12 (1.5)</td>
<td>808</td>
</tr>
</tbody>
</table>

AF = Atrial Fibrillation; BMI = Body Mass Index; LA = Left Atrium; ns = not significant; TIA = Transient Ischemic Attack.
<table>
<thead>
<tr>
<th>Value</th>
<th>Analyzed, N</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>55.0±11.0</td>
<td>59</td>
<td>0.032</td>
</tr>
<tr>
<td>31 (52.5)</td>
<td>59</td>
<td>0.030</td>
</tr>
<tr>
<td>36 (69.2)</td>
<td>52</td>
<td>ns</td>
</tr>
<tr>
<td>13 (28.3)</td>
<td>46</td>
<td>ns</td>
</tr>
<tr>
<td>1.99±0.19</td>
<td>46</td>
<td>0.043</td>
</tr>
<tr>
<td>35 (59.3)</td>
<td>59</td>
<td>ns</td>
</tr>
<tr>
<td>41 (75.9)</td>
<td>54</td>
<td>ns</td>
</tr>
<tr>
<td>3 (6.0)</td>
<td>50</td>
<td>ns</td>
</tr>
<tr>
<td>20 (36.4)</td>
<td>55</td>
<td>ns</td>
</tr>
<tr>
<td>27 (45.8)</td>
<td>59</td>
<td>ns</td>
</tr>
<tr>
<td>14 (23.7)</td>
<td>59</td>
<td>ns</td>
</tr>
<tr>
<td>0 (0)</td>
<td>59</td>
<td>ns</td>
</tr>
<tr>
<td>8 (13.6)</td>
<td>59</td>
<td>0.001</td>
</tr>
<tr>
<td>1 (1.7)</td>
<td>59</td>
<td>ns</td>
</tr>
<tr>
<td>4 (6.8)</td>
<td>59</td>
<td>0.006</td>
</tr>
<tr>
<td>24.2±7.6</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 (1.7)</td>
<td>59</td>
<td>ns</td>
</tr>
</tbody>
</table>
Table 11. Correlations between features of the left atrial appendage and age classifications.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Relative LAA length</th>
<th>Relative LA area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>P</td>
<td>N</td>
</tr>
<tr>
<td>Age as a continuous variable</td>
<td>808</td>
<td>527</td>
<td>&lt;0.001 $^a$</td>
</tr>
<tr>
<td>Non-AF patients</td>
<td>749</td>
<td>481</td>
<td>&lt;0.001 $^d$</td>
</tr>
<tr>
<td>AF patients</td>
<td>59</td>
<td>46</td>
<td>ns</td>
</tr>
<tr>
<td>Over 53 years $^g$</td>
<td>399</td>
<td>266</td>
<td>0.004</td>
</tr>
<tr>
<td>Non-AF patients</td>
<td>362</td>
<td>237</td>
<td>0.009</td>
</tr>
<tr>
<td>AF patients</td>
<td>37</td>
<td>29</td>
<td>ns</td>
</tr>
<tr>
<td>Quartiles according to age $^h$</td>
<td>808</td>
<td>527</td>
<td>0.002</td>
</tr>
<tr>
<td>Non-AF patients</td>
<td>749</td>
<td>481</td>
<td>0.001</td>
</tr>
<tr>
<td>AF patients</td>
<td>59</td>
<td>46</td>
<td>ns</td>
</tr>
<tr>
<td>10-year divisions of age $^i$</td>
<td>808</td>
<td>527</td>
<td>0.007</td>
</tr>
<tr>
<td>Non-AF patients</td>
<td>749</td>
<td>481</td>
<td>0.004</td>
</tr>
<tr>
<td>AF patients</td>
<td>59</td>
<td>46</td>
<td>ns</td>
</tr>
</tbody>
</table>

LA = Left Atrium; LAA = Left Atrial Appendage; ns = not significant.

$^a r=0.156$, $^b r=0.148$, $^c r=0.861$, $^d r=0.162$, $^e r=0.835$, $^f r=0.945$

$^g$ Age median 53 years; patients over 53 years old compared with younger patients

$^h$ Groups: <48 years (26.3%), 48-53 years (24.3%), 54-58 years (23.8%), ≥59 years (25.6%)
Figure 20. Relative left atrial appendage (LAA) length and relative left atrium (LA) area according to the age quartile, with 95% confidence intervals.
5.2.2 Other factors influencing the increase of relative LAA length
In addition to increased age, female gender (2.26±0.48 cm/m² in female vs. 2.09±0.48 cm/m² in male; p<0.001), smoking (2.13±0.48 cm/m² vs. 2.24±0.49 cm/m²; p=0.041) and moderately severe/severe aortic/mitral regurgitation (p=0.038) significantly associated with relative LAA length (Figure 21). After adjustment in the linear regression analyses, age (p<0.001), female gender (p=0.003), and moderately severe/severe aortic/mitral regurgitation (p=0.014), all correlated with an increased relative LAA length, with an adjusted R² value of 0.058.

5.2.3 Factors influencing LAA morphological features other than length
Male patients were more likely to manifest multi-lobed LAAs (p=0.003). A greater number of LAA morphological classes with multiple lobes (i.e. Cactus and WindSock) were seen in overweight patients vs. patients of a normal weight (84% vs. 76%; p=0.010). Other background factors had no statistical influence on morphological classes or the number of LAA lobes (Figure 22).

5.2.4 Factors influencing the increase of relative LA area
Regarding relative LA area, dyslipidemia (10.4±2.9 cm²/m² vs. 9.3±2.3 cm²/m²; p=0.043), a history of AF (11.7±3.2 cm²/m² vs. 9.5±2.3 cm²/m²; p=0.004), calcified and/or stenotic coronary arteries (10.4±2.9 cm²/m² vs. 9.3±2.3 cm²/m²; p=0.045), myocardial infarction (13.5±4.0 cm²/m² vs. 9.6±2.5 cm²/m²; p=0.015), and moderately severe/severe mitral (14.0±1.1 cm²/m² vs. 9.8±2.6 cm²/m²; p=0.045) or aortic regurgitation (15.8±3.1 cm²/m² vs. 9.6±2.4 cm²/m²; p=0.008), were all associated with an increased relative LA area. After adjusting these variables and age in the linear regression analyses, an adjusted R² value of 0.362 was received with a significant association between increased relative LA area and age (p=0.003), a history of AF (p=0.021), a history of myocardial infarction (p<0.001), and moderately severe/severe aortic regurgitation (p<0.001).
<table>
<thead>
<tr>
<th>Category</th>
<th>Total N</th>
<th>Threshold</th>
<th>N (%)</th>
<th>LAA relative length (mm/mm)</th>
<th>LAA length with 95% confidence interval (mm/mm)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>527</td>
<td>≤ 55 years</td>
<td>291 (55%)</td>
<td>21.3±4.6</td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 55 years</td>
<td>236 (55%)</td>
<td>22.7±4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>527</td>
<td>female</td>
<td>349 (66%)</td>
<td>22.6±4.8</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>male</td>
<td>178 (34%)</td>
<td>20.9±4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosed cardiovascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>527</td>
<td>no</td>
<td>238 (45%)</td>
<td>22.2±6.0</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yes</td>
<td>289 (55%)</td>
<td>21.8±4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>527</td>
<td>no</td>
<td>481 (91%)</td>
<td>22.0±4.8</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yes</td>
<td>46 (9%)</td>
<td>22.2±5.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>487</td>
<td>no</td>
<td>446 (92%)</td>
<td>22.1±4.8</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yes</td>
<td>41 (8%)</td>
<td>20.8±3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>487</td>
<td>no</td>
<td>181 (32%)</td>
<td>22.1±4.6</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yes</td>
<td>306 (68%)</td>
<td>21.9±4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>482</td>
<td>no</td>
<td>316 (66%)</td>
<td>22.4±4.9</td>
<td></td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yes</td>
<td>166 (34%)</td>
<td>21.3±4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcified coronary arteries</td>
<td>527</td>
<td>no</td>
<td>299 (51%)</td>
<td>21.0±4.8</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yes</td>
<td>228 (49%)</td>
<td>22.1±4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over 50% stenosis in coronary arteries</td>
<td>527</td>
<td>no</td>
<td>426 (81%)</td>
<td>22.0±4.8</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yes</td>
<td>101 (19%)</td>
<td>22.0±4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>527</td>
<td>no</td>
<td>515 (98%)</td>
<td>22.0±4.8</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yes</td>
<td>8 (2%)</td>
<td>23.8±5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately severe or severe aortic or mitral regurgitation</td>
<td>529</td>
<td>no</td>
<td>516 (98%)</td>
<td>22.0±4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>yes</td>
<td>13 (2%)</td>
<td>24.3±4.7</td>
<td></td>
<td>0.058</td>
</tr>
</tbody>
</table>

*Figure 21. Correlations between relative left atrial appendage length and classification criteria.*
**Figure 22.** Associations between LAA morphological classes and background factors.
5.3 LAA MORPHOLOGY AND CONTRAST AGENT CONCENTRATION IN CCTA PATIENTS WITHOUT ACUTE CARDIOVASCULAR CONDITIONS [III]

The study group was identical with the population of the second publication described in chapter 5.2 and presented in Table 10.

5.3.1 Background factors causing decreased blood flow in LAA based on LAA/LA HU ratio

In the univariate analyses for LAA/AA HU ratio, female gender (0.86±0.14 in females vs. 0.89±0.15 in males; p=0.001), being overweight (0.86±0.16, n=419 vs. 0.89±0.13, n=263; p=0.003), a high BMI value (mean±SD=28.1±5.5, total n=525, r=-0.129; p=0.003), and diabetes (0.84±0.15, n=42 vs. 0.88±0.14, n=698; p=0.029), were all associated with lower values. Figure 23 illustrates these differences regarding gender and overweight.

5.3.2 LAA morphology and LAA blood flow based on LAA/LA HU ratio

The proportions of LAA morphological classes and their LAA/AA HU ratios were: WindSock 62.3% (0.87±0.14), Cactus 18.6% (0.90±0.11), ChickenWing 10.0% (0.89±0.15), and Cauliflower 9.2% (0.84±0.19). Similarly, proportions and LAA/AA HU ratios for the number of LAA lobes were: one lobe (17.0%, 0.86±0.18), two lobes (44.6%, 0.86±0.15), and multiple (≥3) lobes (38.5%, 0.90±0.12). With respect to LAA morphological parameters, only the lobe number was significantly associated with LAA/AA HU ratio; multi-lobed LAAAs displayed increased LAA/AA HU ratios (0.90±0.12 vs. 0.86±0.16; p=0.018). Figure 23 presents the associations between HU ratio and LAA morphological features.

After adjustment of multiple background factors, LAA morphology classes and LA area as covariates into multiple linear regression analyses, only the Cauliflower morphology correlated significantly (p=0.007) with a decreased LAA/AA HU ratio. The dichotomized LAA/AA HU ratios were analyzed with multiple logistic regression analysis with the same covariates. In the final model, only the Cauliflower morphology (OR=4.836; 95% CI: 1.235 to 18.936; p=0.024) proved to be an independent predictor of an LAA/AA HU ratio of less than 0.75. The Nagelkerke R² of the final model was 0.253.
Figure 23. Hounsfield unit (HU) ratios related to the left atrial appendage (LAA) morphological classes, number of LAA lobes, being overweight, and gender, with 95% confidence intervals.
Figure 23 continues
6 Discussion

Despite being an embryologic remnant, the LAA is acknowledged to play crucial part in the process of thrombus formation and thus an involvement in cardioembolic strokes, especially in patients with AF (109). Although the published literature agrees with certain principles, no consensus still exists over the exact morphological features that would predispose to thrombogenesis in the LAA (21,374,378,380,387). Due to its central location, the LAA is being continuously influenced by various systemic attributes, mostly mediated by the LA. The goal of this thesis was to enlarge our current knowledge by examining LAA data derived from patients without a diagnosed AF and therefore, to provide information regarding susceptible morphologies and/or background determinants that might influence the increased stroke risk.

6.1 LAA MORPHOLOGY IN PATIENTS WITH SUSPECTED CARDIOEMBOLIC STROKE WITHOUT A HISTORY OF ATRIAL FIBRILLATION

6.1.1 LAA morphology and stroke
This study compared LAA morphology between patients with acute ischemic stroke of cryptogenic or suspected cardicgenic etiology other than known AF and control subjects without any cardiovascular disease. The prevalence of morphology types (Cactus, ChickenWing, WindSock, or Cauliflower) differed significantly between stroke patients and controls. This difference has been found in the majority of earlier studies, although all but one with AF patients (372,387,390). With respect to LAA morphology, stroke patients in the current study possessed significantly more one-lobed LAAs, which depicts ChickenWing and Cauliflower classes. Both of these classes were also overrepresented in the stroke groups, but only ChickenWing displayed statistical significance. In one of the previous studies, LAAs with multiple lobes have been associated with an increased risk for thrombus due to the tissue’s internal complexity (387). However, in many of the previous studies, Cauliflower has been considered the culprit for increased stroke risk (351,372,376,386). Although it has a complex internal structure, Cauliflower is typically one-lobed and therefore this contradicts the conclusions of Yamamoto et al. According to this scenario, the current study is in concordance with other reports. Nevertheless, substantial remodeling may have affected the lobes and therefore in some studies the characteristics of the lobes may be associated with stroke (381).

The majority of previous results have suggested that non-ChickenWing morphology is associated with thrombus formation and that ChickenWing exhibits the greatest values in flow velocity (352,374,375,384,388,390). This obviously disagrees with the results of the present study. However, the current study examined the coronal angle of the LAA while assessing the amount of LAA bend. In the other studies, measurement of the bend angle was made from the curve of the main LAA lobe or between the main lobe and the secondary lobe.

In concordance with other studies, the LAA takeoff position appeared to be significantly higher in the stroke group; explained by the longer distance of blood flow from the mitral annulus (371,396). Another finding regarding LAA morphology was that LAAs were significantly larger in the stroke group, which is in accordance with previous studies in cardiogenic AF patients and cryptogenic stroke patients (211,212,376,383,390). Despite the apparent discrepancy with a short Cauliflower morphology, longer LAAs do not necessarily possess the highest volumes since they may be larger in some other
dimension. One could hypothesize that the remodeling process may have damaged the LAA internal wall structure and thus enlarged its original volume. In AF patient studies, remodeling has been claimed to be a consequence of dilatation, reduction in the pectinate muscles and forming of fibroelastosis (15,367). In non-AF patients, however, the remodeling process could be initiated by an activation of RAAS (e.g. in heart failure), excessive amount of pericardial fat or cardiac infections (224,225,243,357,358,397,398). The current study found that Cauliflower possesses the lowest volume and that stroke population has higher LAA volumes than controls. This apparent contradiction is attributable to volume differences in the LAA between the two study groups’ morphological classes, i.e. class-wise volumes differed significantly. As presented in the review section, previous study results disagree regarding the smallest LAA class (372,375,390).

6.1.2 Evaluating the LAA morphological classification
In 2010, Wang’s model provided the first method to classify LAAs in a more versatile way. The popularity of the model may be based on both its originality and simplicity; instead of multiple classes and possible subclasses, this model has only four options. However, the original research explained the classification scarcely by saying: “The general LAA morphology could be first classified based on the following kinds: (1) LAA with sharp bend (ChickenWing type, 18.3%). (2) LAA without sharp bend.” The introduction of other three classes seemed arbitrary. (151) Two years later, Di Biase (a researcher in the same group) claimed that non-ChickenWing morphology increased the risk for stroke in patients with AF. The possible pathophysiological mechanism was not dealt with in the discussion. Moreover, the LAA velocity of the ChickenWing did not differ from other morphologies. (390)

As in most of the preceding studies, the present study used Wang’s classification to assess the LAA morphologies. The majority of previous studies evaluated LAAs purely based on visual appearance, which in some cases, can introduce a judgement bias even with a consensus-reading. In an attempt to introduce more objectivity, Kimura’s quantitative criteria were utilized. The three observers in the current study, reproducibility reached a good level but this was nonetheless far from excellent (Cohen’s kappa value of 0.65). In other studies, the agreement level has been highly variable (κ value range: 0.346-0.84), and also the proportion of LAA classes has been divergent (378,380,386,390). Although most stroke-related LAA studies consider non-ChickenWing as a potential stroke candidate, one should not overlook the possibility of research confirmation bias. Therefore, the current classification seems to lack consistency for practical use, at least without the introduction of reliable quantitative measurements.

6.2 INFLUENCE OF BACKGROUND FACTORS ON LAA MORPHOLOGY AND LEFT ATRIUM IN NON-STROKE PATIENTS

6.2.1 Age
The present study found no direct connection between aging and LAA morphological features, in agreement with previous studies examining healthy patients. However after adjusting LAA length with the BSA value, a positive correlation was established, which agrees with the conclusion presented by Boucekci et al. of the correlation with LAA volume but disagrees with the results of Veinot et al. regarding LAA length (19,170). Interestingly, this result applied only to the non-AF population and not to patients with AF. One explanation may be the remodeling effect of AF, which reduces the differences attributable to different ages. In addition to changes in the LAA, age positively correlated with relative LA area in the overall study population. In AF patients, the association appeared with age as a
continuous parameter, which may be explained by the same remodeling effect of AF as
with LAA. Nonetheless, the earlier results regarding age and LA size are contradictory; in
healthy patients, one study suggested that there was an association with LA diameters but
not explicitly with LA volume, in another no correlation with LA volume and yet another
detected a decrease in the LA volume. The mean ages differed in these studies (58yr, 76yr
and 49yr, respectively), which may account for some of the discrepancies. Apart from the
current study, these other publications utilized either CMR or TTE. (327,355,356) Two other
studies in patients in sinus rhythm but with some cardiovascular burden suggested that
either LA volume or LA dimensions increased with age; paralleling the current study with
regard to population and outcomes (353,354). Based on all these results, it seems that LA
increases with age only if there is some underlying pathological dysfunction (399).

LAA wall and other components of the cardiovascular system are susceptible to
deterioration with age. This remodeling may increase the risk for thrombosis as the
frequency of embolic events has been associated with increasing age (7). The current study
confirms that age-related remodeling of LA and LAA occurs also in patients without the
impact of AF.

6.2.2 Gender and weight
The differences between genders have been studied previously to some extent. The current
study confirmed one of the previous studies i.e. that men have longer LAAs than women
(170). In addition, men possessed larger LA areas, one possible reason for their longer
LAAs. BSA, but not overweight or obesity, positively correlated with LAA length. The
BSA-indexed LAA lengths, in turn, revealed that women possess longer LAAs. This finding
is in contrast with the studies of Boucebci et al. and Veinot et al., as well as with the
evidence that men have a greater proportion of multi-lobed LAAs (19,170). Veinot
considered that none of the body measurements had any impact on LAA dimensions (19).

Concerning the number of lobes between genders, after excluding patients with
normal body mass, the association was lost. Furthermore, since overweight patients also
possessed more multi-lobed LA morphologies in the current study, one might speculate
that the amount of epicardial fat may influence the number of LA lobes. Thus, the more
multi-lobed LAAs may be a visually accessible feature that relates to remodeling in obese
individuals. The remodeling impact of epicardial adipose tissue has been previously
confirmed and is known to decrease LAAEF, but other studies lack information regarding
the number of lobes (358).

6.2.3 Medical conditions
None of the non-stroke patients’ medical conditions (hypertension, dyslipidemia, diabetes,
history of smoking, AF, coronary artery calcification or stenosis, prior MI, prior stroke/TIA,
mitral or aortic valve regurgitation, heart failure) were associated with the number of LAA
lobes, paralleling the current literature. Patients with AF had significantly longer LAAs
than non-AF patients and, also in concordance with previous studies, patients with AF
possessed substantially greater LAs (369). It is not fully clear whether AF patients possess
longer LAAs than non-AF patients, although a difference in LAA volumes has been
recognized between these groups (367,372,380). However, short term AF does not seem to
cause LA or LAA remodeling (400). Sustained or prolonged AF may elongate the LAA due
to an indirect effect originating from the enlarged and more voluminous LA, but probably
also directly by affecting the orifice size (348,366). Ultimately, remodeling causes an
expansion of the LAA luminal area (15,367). Interestingly in the current study, the
difference in LAA lengths between AF and non-AF population disappeared after LAAs
were indexed with BSA; moreover, the LA size lost its association with LAA length.

Patients suffering from CAD and moderately/severe mitral/aortic regurgitation had
longer LAAs, but only regurgitation appeared to be statistically significant after adjustment
for BSA and evaluated with linear regression analysis. With regard to the relative LA area,
both mitral and aortic regurgitation, CAD, prior MI and dyslipidemia displayed a positive correlation. There is no clear evidence of any direct association with left side valve regurgitation in the current literature, but one could speculate that the mechanism would be attributable to the continuously elevated pressure in the LA (363,365). This is also supported by the similar conditions affecting the size of the LA, which is considered to be a volume sensor in the heart as it reacts to increased internal pressure by excreting ANP and BNP. Moreover, other factors (history of MI, CAD) causing LV diastolic dysfunction and, thereby influencing LA size, have been recognized in previous studies (401-403). In particular, LA volume is considered to possess predictive value with respect to cardiovascular disease and to be a prognostic marker in CAD (403).

6.3 INFLUENCE OF LAA MORPHOLOGY AND BACKGROUND FACTORS IN CONTRAST AGENT ATTENUATION IN NON-STROKE PATIENTS

6.3.1 LAA morphology
One key study finding was that short and one-lobed LAAs were associated with decreased LAA/AA HU ratios. To date, only the current study has examined this property in terms of HU ratios in non-acute-stroke non-AF patients, although only one previous study examined exclusively non-AF patients (316). These short and one-lobed LAAs represent the Cauliflower class in Wang’s classification and they displayed the only connection to the HU ratio after adjustment of multiple regression analysis. As discussed earlier, many previous studies have indicated that either non-ChickenWing or Cauliflower are the most susceptible morphologies promoting the formation of thrombi in AF patients (21,351,352,372,375,376,388). In agreement with a previous study in AF patients conducted by Kelly et al., the current study found no difference between non-ChickenWing and ChickenWing morphologies regarding HU ratios (383). The attenuation ratio of HU reflects the blood flow in the LAA and thus this finding suggests that on average, the blood flow in Cauliflower LAA is less intense than in other LAA classes, as noted by Lee et al. in AF patients (376). According to this result, Cauliflower morphology may possess an innate feature capable of causing a low flow profile, independent of the effect of AF. Lee et al. speculated that the impact of Cauliflower resulted from the larger orifice size and lower flow velocity (376). Furthermore, Lee et al. claimed that Cauliflower not only displayed low-amplitude flow velocity profile compared to ChickenWing, but also the largest orifice and most voluminous structure (375). Despite the compelling straightforward logic, some studies agree and some disagree about the link between orifice size and LAA volume (212,372,376,390). Unfortunately, the current study lacked the information regarding LAA volume and orifice size.

To date, the current study seems to be the only report investigating HU ratios among non-stroke and non-AF patients. By revealing the variability of LAA/AA HU ratios in a general, non-AF population, these results can be utilized as reference values in future studies. In addition, because of TEE’s semi-invasive nature, CCTA could serve as an alternative assessment tool for LAA blood flow. Low HU ratio values may also parallel SEC and, thus, these findings in CCTA would justify control with TEE.

6.3.2 Background factors
The present study found no independent background factors, which would predict the LAA/AA HU ratio. In univariate analysis, female gender, diabetes and overweight were associated with decreased HU ratio values. Obesity and female gender are known to increase epicardial adipose tissue and the amount of tissue has been correlated negatively with LAA/AA HU ratio (358,404). In the study conducted by Tsao et al., the abundance of epicardial fat was also associated with an increased stroke risk in AF patients (358). Diabetic patients, in turn, possess larger LA dimensions, which are thought to correlate
negatively with the LAA flow velocity (199,202,405-407). From this perspective, the current study results are in line with previous studies and, although not independent predictors, they might offer an explanation for the indirect impact on LAA flow in non-AF patients and the increased risk for clot formation.

6.4 STUDY LIMITATIONS

The stroke population included a relatively small number of patients, which may be considered as its main limitation. The ESUS criteria were not available at the time of recruiting and thus the population selection contained greater heterogeneity. Moreover, complete exclusion of AF was not possible, because PAF is not invariably recognized with 24h ECG monitoring (408). The study follow-up lasted only 3 months and therefore, late-onset AFs or strokes were not identified.

The other two studies comprised a large cohort, but only one observer evaluated the LAA morphologies and HU ratios in the majority of scans. However, there was a second observer who measured the HU values of 97 consecutive patients and it was found that the inter-observer reproducibility appeared to be good regarding LAA morphologies and excellent with respect to HU ratios.

The CCTA study population contained more women and the subgroup of AF patients was rather small. Unfortunately, the control patients suffered from various background diseases and therefore they may not be fully considered as a healthy population. Although healthy subjects would have been the optimal population, the lack of a clinical indication that would require imaging would have made CT scans unethical. The study lacked information on LAA volume, thickness and orifice size, LA volume and ejection fraction, and LV characteristics. In addition, heart rates and blood pressures were not collected during the scans. The weight status was assessed retrospectively, i.e. the BMI values were not necessarily registered at the exact time of CCTA. In the CCTA images, the presence of calcified coronary arteries complicated the assessment of stenosis. Patients were imaged during mid-diastole, which is a non-optimal phase if one wishes to evaluate the maximal LAA lengths or compare HU values with LAAFV. With regard to the original imaging indication, end-systolic images would not have had any diagnostic value and therefore would not have been justifiable. In addition, LAAFVs are typically measured by the LAA ostium area rather than the tip of the LAA, which complicated the comparison with other studies (409).
7 Conclusions

The following conclusions can be drawn from the individual studies (I-III) in this thesis:

1. LAA morphological classification differed between the stroke population and healthy controls. One-lobed and high-voluminous LAAs were overrepresented among these stroke/TIA patients. The use of the LAA morphological classification devised by Wang et al. seems inconsistent; this is reflected in the extensive variability in inter-observer reproducibility among studies; thus it lacks clinical feasibility in its current form. (I)

2. In this large non-stroke population, body size indexed LAA length correlated positively with aging. Furthermore, females possessed increased relative LAA lengths and males exhibited an excess of multi-lobed LAAs. Being overweight associated with LAA morphological classes with more lobes. (II)

3. With respect to attenuation ratio of the contrast agent, patients with short and one-lobed LAA morphology displayed lower values, which reflects the decreased blood flow in the LAA. (III)
8 Future perspectives

Since carotid artery CTA is routinely performed in stroke patients, combining cardiac CT is straightforward and useful for assessing potential LAA thrombus and LAA morphology. Moreover, LAA morphology and its filling properties may be evaluated in patients undergoing CCTA with a low or moderate pretest probability for CAD. These LAA related factors are thereby simultaneously accessible and provide useful reference data regarding non-stroke patients.

The current generalized division into four morphological classes (ChickenWing, WindSock, Cauliflower, Cactus) is convenient but the interobserver reproducibility exhibits inconsistency. Confining the studies so that they would have been only restricted to the classification could well have obscured the identification of meaningful features with regard to increased stroke risk. As the development of imaging technology continues to advance by leaps and bounds, studies on LAA morphology will become more accurate and versatile. Combining the assessment of concurrent flow properties with 4D flow CMR appears to be especially promising and may represent a potential step in resolving more of the fundamental properties of the LAA.

Recent studies regarding LAA morphology have mostly concentrated on patients with AF. Despite the value of these works, more information on LAA characteristics and their relationship to ischemic stroke should be gathered also in other cohorts (e.g. ESUS vs. non-ESUS patients) and from various age groups. Concurrently, the short- and long-term prognosis regarding LAA morphological features and LAA functionality, especially in ESUS patients, should be evaluated with systematic, high-quality research incorporating the setting of meaningful endpoints (ischemic stroke/TIA, systemic embolization). In addition, the post-stroke prognosis related to certain LAA features and neurological findings should be assessed in the future. Concerning the antithrombotic therapy relating to LAA morphological features, comparing the effects of aspirin and NOAC in randomized mixed trials would offer an interesting clinical perspective in the ESUS group.

In the current study in non-AF non-stroke patients, Cauliflower morphology exhibited a significant decrease in the LAA/AA HU ratio, indirectly reflecting poorer blood flow in LAA. Nonetheless, it is not clear if any LAA morphological feature itself can be categorized as hazardous and would be able to cause LAA thrombus without the burden of some pathological condition. For example, some surgical removals of LAA are performed simultaneously with cardiac procedures and it would be important to know if removal of a certain type of LAA would be beneficial or not. Evaluating the innate nature of LAA related to the risk for thrombus would require large systematic follow-up studies in low-risk patients who suffer from suspected cardioembolic stroke; however, the outcome would be of clinical value.
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Stroke is a major global health risk causing mortality and long-term disability. A cardiogenic etiology accounts for one out of every five ischemic strokes and the left atrial appendage (LAA) is considered to be the most important source of cardiac emboli. This thesis attempts to reveal the morphological features of the LAA that might predispose to cardioembolic stroke and to evaluate the impact of background factors on LAA morphology and blood flow in non-stroke patients by utilizing computed tomography.