



# Left atrial appendage closure: prevalence and risk of device-associated thrombus formation

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There remains no doubt that atrial fibrillation (AF) is associated with an increased stroke risk (1). It is also clear that the vast majority of thrombi in patients with non-valvar AF are located in the left atrial appendage (LAA) (2). Multiple randomized trials have demonstrated a mortality and stroke rate reduction with anticoagulation using a vitamin K antagonist (3). More recently, the superiority of LAA closure using a nitinol cage (Watchman device) over anticoagulation with a vitamin K antagonist has been shown regarding all-cause mortality (driven by a lower rate of intracranial hemorrhage), disabling strokes and long-term bleeding (disregarding the up-front rate of pericardial bleeding) (4). Therefore, in most countries, LAA closure has established itself as the treatment of choice in patients with a high or prohibitive bleeding risk, despite the fact that its utility has been shown in a different patient population, those with a low bleeding risk who are able to tolerate anticoagulation. Optimally, a LAA closure device would seal the LAA completely leaving no potentially thrombogenic LAA tissue behind and not cause thrombus formation both of which may diminish and, perhaps, off-set the (stroke prevention) benefits of the procedure. The reality is that neither applies to the current technology. In fact, regardless of the device or trial, device-associated thrombus formation (DTF) has been reported. It has been less clear if and to what degree the discovery of this finding increases the stroke risk. Previously, based on the observed device-associated thrombus rate of 20/478 patients (4.2%) in PROTECT-AF of whom 3 had a stroke prior to detection, the device-thrombus

associated stroke risk has been estimated to be 0.3% per 100 patient years. In other words, it has been assumed that the risk of stroke caused by DTF per year is only 0.3% (5). From a different perspective, however, one could assume that the risk of a stroke in the presence of DTF is at least 3/20 (=15%) not taking into account that some of the other reported strokes at follow-up may have been related to unknown DTF (or thrombi no longer seen on the device as they have embolized). Hence, the DTF rate has not received as much attention as it, perhaps, should. Therefore, the findings of the recently published manuscript by Fauchier *et al.* in the *Journal of the American College of Cardiology* are very important (6). Data from 469 consecutive patients who underwent LAA closure, in the overwhelming majority with the Watchman device, Amplatzer Cardiac Plug or Amulet, were retrospectively analyzed with focus on the incidence and consequence of DTF.

First, data confirm previous findings of DTF with an incidence for the Watchman device (5.5%) similar to that previously reported in an analysis of several publications (2–6%) (7) and for the Amplatzer Cardiac Plug/Amulet device (11%) also similar to that reported in prior analyses (2–18%) (7). Of note, this numerical difference between the devices did not reach statistical significance. It should be mentioned that the accuracy of imaging for thrombus detection has not been validated; distinction of thrombus versus pronounced endothelialization or tissue proliferation is not always clear (8) and the true incidence of DTF may, hence, be over- or underestimated.

Second, and more importantly, the authors also confirm our suspicion that DTF is not a finding to be complacent about because the stroke/systemic embolism rate is higher than if no thrombus is present. Of the 26 patients who were found to have DTF, 4 (15%) had a stroke compared to 10 of 313 (3%) who did not have DTF (adjusted hazard ratio: 4.4,  $P=0.04$ , on multivariable analysis DTF was an independent risk factor for stroke apart from age and prior history of stroke). Incidentally, the stroke rate (15%) in those patients with DTF was no different from the aforementioned 15% observed in patients with DTF in the PROTECT-AF trial. Though the statistical power to prove that DTF may cause cerebral or systemic embolic events and that the risk of these events is higher in patients who are found to have DTF was limited in this study, it supports our concept of pathophysiology, that intravascular or intra-cardiac thrombi can cause embolization and are, therefore, potentially dangerous. Nevertheless, the findings should not be misused to prematurely discredit an effective procedure but should be viewed in the following context: the alternative to LAA occlusion, anticoagulation, also does not eliminate the risk of LAA thrombus. In patients on therapeutic anticoagulation for AF while undergoing transesophageal echocardiography for planned ablation, the reported rate of LAA thrombi remains 0.3–3.6% (9-16). This risk will not diminish over time during anticoagulation, whereas the risk of DTF is likely to decrease after device endothelialization. Moreover, the prevalence of LAA thrombus is much higher in patients with AF who are not or inadequately anticoagulated. For example, the prevalence of LAA thrombus was 12% in 600 patients with AF of <48 hours duration whose anticoagulation was subtherapeutic and 15% in a study combining transesophageal echocardiography and autopsy data (17). Most importantly, despite the potential for DTF, the event rate after LAA closure has been very low in both randomized trials and a number of large registries, thus supporting its efficacy (4,18-20).

How can we avoid DTF? To answer this question, a better understanding of what causes or promotes it is needed. In the meantime, intuitively, one would suspect the usual suspects, a thrombogenic endovascular surface, stasis and blood thrombogenicity. A thrombogenic endovascular surface is likely to remain at least until, and maybe beyond, complete endothelialization. How long does complete endothelialization take? In an animal (dog) model, this takes approximately one month (21). However, the speed of endothelialization in humans is not known and is difficult to study on a larger scale. In one study of

four humans who underwent an autopsy, on average, 417 days after the procedure, the device appeared to have been covered with endocardium (21). Whether consistent endothelialization occurs within the first few months after implantation in humans is unknown. In this context, assessing endothelialization based on permeability of the device after implantation by CT scanning in patients who did not have a peri-device leak (assessed by transesophageal echocardiography), incomplete endothelialization was reported in 61% at a mean follow-up of 10 months (22) thereby suggesting that it may take longer than previously thought. Stasis may promote thrombus formation in AF. The observed higher stroke rates in patients with AF and mitral stenosis (23) and lower than expected rates in those with AF and mitral regurgitation (24) support this notion. Spontaneous echo contrast (SEC), an indicator of stasis, is an independent predictor for strokes in AF (25). Similarly, a reduction in LAA peak flow velocities, a surrogate for stasis, is an independent risk factor for stroke in patients with AF (26,27). Though the relationship between stasis and thrombus formation has only been shown in patients with AF who have not undergone LAA closure, it is likely that this would contribute to DTF. Thrombogenicity, i.e., the propensity of a patient's blood to clot, is difficult to gauge. Parameters that may be associated with thrombus formation are frequently elevated in patients with AF. Fibrinogen (28), prothrombin fragments 1 and 2 (29), D-dimers (28), thrombi-antithrombin complexes (29), platelet microparticles (30), beta-thromboglobulin (28) and von Willebrand factor (31) are examples. In other words, AF may be associated with a "prothrombotic" state. Moreover, some parameters [e.g., D-dimer level, von Willebrand factor (vWF)] may predict the presence of LAA thrombus or clinical events regardless of treatment with anticoagulation (32-35). Furthermore, gene polymorphisms of the coagulation system [e.g., fibrinogen (36,37), factor XIII (38)] as well as of platelet function [e.g., integrin alpha 2 (39)], by virtue of increased prothrombotic agents (38), may cause a higher risk of thrombus formation (37) or clinical events (39) in patients with AF. Once again, whether this also applies to DTF is not clear. Some inflammatory mediators [e.g., C-reactive protein (CRP), soluble intercellular adhesion molecule-1 (sICAM-1), fibrinogen, interleukin 6 (IL-6), tumor necrosis factor (TNF)-alpha, CD-40 ligand] have been found to be elevated in patients with AF (40-44) and may promote LAA (and, perhaps, device-associated) thrombus formation. These aforementioned risk factors for LAA thrombus may, in the future, predict the propensity of a patient to

develop DTF. However, even if it was possible to predict the likelihood of DTF (for example, by characterizing patients regarding stasis and thrombogenicity), what would be the therapeutic consequences? If patients classified at high risk of DTF should be treated differently, how should they be treated? One might imagine that anticoagulation with vitamin K antagonists or direct anticoagulants or heparin (e.g., enoxaparin) would be more likely to prevent thrombus formation than antiplatelet therapy. However, though not compared head-to-head in a randomized clinical trial, there are mixed results from available data with some studies suggesting no difference in the incidence of DTF regardless of treatment (double antiplatelet therapy, vitamin K antagonists or direct oral anticoagulants) (45,46). Not to mention that early treatment with anticoagulants may be associated with a higher risk of pericardial bleeding/effusion. Therefore, even if correct identification of patients at risk for DTF were possible, we currently do not know what the preventive/therapeutic consequence should be, other than that we do know that single antiplatelet therapy or no antiplatelet/anticoagulant therapy after device implantation, from the perspective of DTF, is not as safe as dual antiplatelet therapy or anticoagulation (the use of dual antiplatelet therapy or anticoagulation after the procedure had a protective effect regarding DTF in the study published by Fauchier *et al.*). Though it appears that DTF may not be benign, it remains to be determined if thrombus location, size and morphology matters. For example, it is conceivable that a small layered thrombus at the device LAA transition has a different embolic risk than a large mobile thrombus.

Third, the clinical event rate (death: 6.9%, ischemic stroke: 4.0%, major hemorrhage: 3.8%) at just over 1 year (mean follow-up 13 months) was higher than reported in the pivotal randomized trial [e.g., death and ischemic stroke per 100 patient-years was 3.0% and 2.2%, respectively, in the device group in PROTECT-AF (47)]. The reason for this is not clear. However, it is likely, at least in part, related to the patients' baseline characteristics. For example, in PROTECT-AF, the mean age in the intervention group was 72 years, the incidence of prior transient ischemic attacks or strokes 18% and none of the patients were considered to have a contraindication to anticoagulation. This compares with a mean age of 75 years and incidence of prior ischemic strokes of 41% and a proportion of patients considered to have a contraindication to anticoagulation of 73% in Fauchier *et al.*'s study. Under real world circumstances, given the overall poorer health, a higher rate of adverse events is to be expected. This is also

supported by data from other larger registries. For example, in EWOLUTION, at one-year follow-up in the just over 1,000 patients who underwent LAA closure included in this registry, the mortality was 9.8% (18). Hence, in real life, the expected bench mark regarding outcomes after LAA closure should be adjusted according to patients' baseline health.

In conclusion, the authors are to be commended for systematically examining the prevalence and relevance of DTF. The data was acquired without support from industry. It suggests that this phenomenon remains common and should not be taken lightly. It would seem that surveillance imaging (e.g., echo or CT) would be prudent in the period when no or incomplete endothelialization is anticipated. However, when, how often and how long this surveillance is necessary is unclear. It further advocates the temporary use of double antiplatelet therapy or anticoagulation in those patients who are likely to tolerate it. Finally, it demonstrates that in a real-world population, a high adverse event rate including death is to be expected due to the patients' baseline age and co-morbidities.

Where to go from here? To further understand the pathophysiology of DTF and its implications as well as preventive strategies we should focus on further study of echocardiographic, clinical and biochemical risk factors in a prospective fashion, examine which thrombi are associated with the highest risk and determine in a prospective, optimally randomized, trial what the best preventive (and therapeutic) strategies may be. Meanwhile, device manufacturers should continue to explore designs that reduce thrombogenicity.

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### Footnote

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