Device-Related Thrombus After Left Atrial Appendage Closure

Philippe Garot, Bertrand Cormier and Jérôme Horvilleur

Hôpital Privé Jacques Cartier, Institut Cardiovasculaire Paris Sud – Ramsay Générale de Santé, Massy, France

Abstract
Although left atrial appendage closure (LAAC) has proved non-inferior to oral anticoagulants in patients with AF, there has been recent concern about the occurrence of late complications, especially device-related thrombus (DRT), which was associated with increased risk of stroke. In this article, the incidence, risk factors and time course of DRT after LAAC are discussed, as well as the potential benefits of dedicated strategies in the management of DRT, which remain speculative, especially in patients with a contraindication to oral anticoagulants. In these patients, decision-making should be based on a multidisciplinary evaluation of the ischaemic/bleeding balance on an individual basis.

Keywords
Complications, device-related thrombus, left atrial appendage closure, outcomes, stroke, thrombus

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Correspondence: Philippe Garot, Hôpital Privé Jacques Cartier, Institut Cardiovasculaire Paris Sud, 6 Avenue du Noyer Lambert, 91300 Massy, France.
E: p.garot@icps.com.fr

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Left atrial appendage closure (LAAC) has been shown to be non-inferior to warfarin in decreasing the risk of stroke and systemic embolism in patients with AF. In addition to peri-procedural complications (tamponade, device migration, procedure-related stroke or embolism, and vascular complications), there has been growing concern recently about the occurrence of late complications, especially device-related thrombus (DRT).

Although DRT has been previously reported in patients enrolled in the Watchman® Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) trial, the incidence, predictors and outcomes of DRT have been recently described in a larger population of 1,739 patients who received a Watchman® device, using data from two randomised trials (PROTECT AF and Evaluation of the Watchman® LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy [PREVAIL]) and two registries (Continued Access to PROTECT [CAP] and Continued Access to PREVAIL [CAP2]).

Incidence, Consequences, Risk Factors and Time Course of Device-Related Thrombus

The global incidence of DRT in patients with AF treated by LAAC has been reported to be 3–7%. Interestingly, DRT has been associated with an average threefold increased risk of stroke or systemic embolism, as well as a greater risk of bleeding, whereas the risk of cardiovascular and all-cause death was not different from that of patients without DRT. However, most patients with DRT did not have a stroke or systemic embolism. Indeed, the vast majority of strokes after LAAC (approximately 90%) occurred in patients with greater risk factors for stroke in general, and who had no evidence of DRT. Nevertheless, there is a probable causal relationship between DRT and stroke or systemic embolism, since a stroke has been reported to occur within 2 months of DRT detection in a non-negligible proportion of patients (nearly 50%) who had DRT and stroke.

Risk Factors for Device-Related Thrombus
There is clear evidence that the risk of DRT is not equal for all LAAC recipients. The risk of DRT is higher among those with larger left atrial appendages, a history of stroke or transient ischaemic attack, permanent AF, lower ejection fraction and vascular disease. Interestingly, these conditions are associated with a higher risk of cardiac and arterial thrombosis, and some are components of the CHA₂DS₂-VASc score.

Some instances of DRT are also related to procedural characteristics, since the uncovered area of the left atrial appendage after deep implantation has been shown to be instrumental in thrombus formation. The question of whether DRT could be related to the post-procedural drug regimen is more controversial. On one hand, most DRTs with the Watchman device have developed after oral anticoagulant discontinuation, but on the other there are multiple observational registries showing that not only dual but also single antiplatelet therapies appear to be a safe option after LAAC, especially in patients with absolute contraindications to anticoagulants.

Time Course of Device-Related Thrombus After Left Atrial Appendage Closure
The time course of thrombus development after LAAC is not clear since DRT is mostly silent, and the imaging protocol follow-up differs from patient to patient. While some instances of DRT were reported within the first weeks after implantation, others were observed several months later. The time course of thrombus development after LAAC is not clear since DRT is mostly silent, and the imaging protocol follow-up differs from patient to patient. While some instances of DRT were reported within the first weeks after implantation, others were observed several months later.
from one study to another. Dukkipati et al. reported that most DRTs (>80%) were detected beyond 45 days after LAAC procedures. DRT was detected in 13 of 1,706 patients (0.8%) at 45 days, in 12 of 692 (1.7%) at 6 months and in 27 of 1,504 (1.8%) at 12 months. It is noteworthy that in the randomised trials, transoesophageal echocardiography (TOE) was performed at 6 weeks, 6 months and 1 year, while the follow-up was lighter in all published observational registries. Consequently, registries reporting the lowest rate of DRT were, not surprisingly, those that had no predefined imaging follow-up beyond 6 weeks, as well as those without core lab examination.

Given that the time required for device sealing may vary depending on patients, devices and procedures, it is particularly difficult to design one method of imaging follow-up for all patients. US Food and Drug Administration-designed trials have proposed a 6-month follow-up TOE to potentially detect more DRTs but the ideal protocol has yet to be designed. Very late (>1 year post-procedure) DRT has not been assessed and is thought to be less frequent because of device sealing, which remains variable on an individual basis. However, in keeping with our observations regarding late coronary stent thrombosis, caution is warranted in the presence of stroke or systemic embolism >1 year after LAAC, and TOE should be repeated in these patients.

**What We Do Not Know and What Is Speculated**

**Potential Unknown Risk Factors for Device-Related Thrombus**

In addition to the patient- and procedural-level characteristics that have been reported as potential risk factors for DRT, certain general clinical conditions usually associated with thrombosis may well play a role in DRT, such as chronic renal failure, diabetes and hypercoagulability status. Inter-patient response variability to antiplatelet agents has been described after stent thrombosis. Although unproven in the setting of LAAC, it is probable that DRT is more likely to occur among poor responders to antiplatelet drugs.

Concern has been raised that certain design characteristics of the device may trigger the development of DRT, such as the protruding central screw being potentially associated with delayed sealing. In the absence of any comparison between the Watchman and Amplatzer™ devices, we cannot conclude whether either of these devices carry an adverse risk of DRT. However, companies have developed strategies to facilitate device sealing, which could result in a decreased rate of DRT.

**Should We Manage Patients with a High Risk of Device-Related Thrombus Differently?**

Whether patients at greater risk of DRT should be managed differently is questionable. Better screening and more aggressive drug regimens and DRT detection strategies are potentially beneficial in this subset of patients. DRT develops during the sealing process, before re-endothelialisation has been achieved. Oral anticoagulant and/or antiplatelet agents are given for several months to prevent thrombus formation.

We have learned from PROTECT AF and PREVAIL that TOE at 6 months resulted in the detection of more cases of DRT; however, no benefit was evidenced using this strategy in terms of stroke rate reduction in the whole population. Case reports have shown DRTs resolving with adequate anticoagulation over several months, which should encourage increased surveillance after LAAC.

Several options should be pointed out, such as postponing the 6-week follow-up TOE to 3–6 months post-procedure, or carrying out more aggressive TOE monitoring in patients at high risk of DRT; however, the latter exposes them to greater discomfort, as well as the risks inherent in additional transoesophageal examinations. In this setting, the benefit of using CT to detect a thrombus should be underlined because repeated TOE assessments are uncomfortable for patients and a potential source of complications.

One of the issues related to DRT is that reintroducing anticoagulants is associated with a high bleeding risk. Consequently, preventative and curative options are quite scarce in patients with a contraindication to oral anticoagulants. The answer to the question as to whether the contraindication is “relative” or “absolute” is obvious, and decision-making about DRT management should be based on a multidisciplinary evaluation of the ischaemia/bleeding balance on an individual basis.

The appropriate management of patients at low and high risk of DRT is yet to be defined because of the relatively low rate of DRT and ischaemia-related complications. Among 1,739 recipients of a Watchman device, Dukkipati et al. reported nine strokes in 17 patients with DRT. Although potentially underestimated, this should be given careful consideration in view of the risk and the consequences of bleeding in these patients.

The use of direct oral anticoagulants, which have been associated with a lower intracranial haemorrhage risk, should be evaluated as a curative strategy for DRT as well as a potential preventive strategy in patients at high risk of thrombosis. Similarly, the role of P2Y₁ inhibitors (ticagrelor, prasugrel), which have the potential to better inhibit platelet aggregation compared with clopidogrel, on the surface of the device during the sealing process should be evaluated for safety/efficacy in patients at high-risk of DRT and for those with documented high on-treatment platelet reactivity.

Although patients treated with anticoagulants/LAAC for AF are still exposed to risks of recurrent stroke and bleeding, there could be different strategies according to the higher ischaemia/bleeding risk. In patients with a higher ischaemic risk, additional imaging follow-up might be helpful, given that shorter bleeding treatment should be preferably selected in those with a higher bleeding risk.

Clearly, uncertainties remain in the management of DRT, including imaging follow-up, prevention and treatment, especially in patients with a contraindication to oral anticoagulants. Since more aggressive TOE surveillance and oral anticoagulant/antiplatelet strategies are not associated with any proven clinical benefits, whether we should implement dedicated strategies in these patients remains speculative and should be considered on an individual basis.

**Conclusion**

The incidence of DRT after LAAC is relatively low (3–7%) and it is more likely to occur in patients with a documented high risk of DRT and after inadequate device positioning. DRT is associated with an average threefold increase in the risk of stroke. In the very high-risk subset of patients with a contraindication to oral anticoagulants, this complication should be weighed up against the risk of non-DRT related stroke, bleeding and intracranial haemorrhage.
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