Thrombogenicity and antithrombotic strategies in structural heart interventions and non-aortic cardiac device therapy – current evidence and practice

Theme issue review

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Abbreviations

ACT	Activated clotting time
AFIB	Atrial fibrillation
ASA	Acetylic salicylic acid
CAD	Coronary artery disease
CF-LVAD	continuous-flow LVAD
DAPT	Dual antiplatelet therapy
DRT	Device-related thrombosis
DTI	Direct thrombin inhibitor
EHRA	European Heart Rhythm Association
HF	Heart Failure
ICD	Implantable cardioverter-defibrillator
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
LAA	Left atrial appendage
LAAO	Left atrial appendage occluder
LVAD	Left ventricular Assist Device
NOAC	Non-Vitamin- K antagonist Oral Anticoagulants
OAC	Oral anticoagulation
PFO	Patent foramen ovale
SAPT	Single antiplatelet therapy
TAVR	Transcatheter Aortic Valve Replacement
TMVR	Transcatheter Mitral Valve Replacement
TOE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
UFH	Unfractionated heparin
VKA	Vitamin K Antagonists
vWF	von Willebrand factor

Abstract

As the number of, and the indications for structural heart interventions are increasing worldwide, the optimal secondary prevention to reduce device thrombosis is becoming more important. To date, most of the recommendations are empiric. The current review discusses mechanisms behind device-related thrombosis, the available evidence with regard to antithrombotic regimen after cardiac device implantation as well as providing an algorithm for identification of risk factors for device thrombogenicity and for management of device thrombosis after implantation of PFO and LAA occluders, MitraClips/TMVR, pacemaker leads and LVADs. Of note, the topic of antithrombotic therapy and thrombogenicity of prostheses in aortic position (TAVR, surgical mechanical and bio-prostheses) is not part of the present article and is discussed in detail in other contemporary focused articles.

Keywords: patent foramen ovale, left atrial appendage, MitraClip, left ventricular assist device, device related thrombosis

Introduction

Following device implantation, thrombotic events associated with cardiac devices can be attributed to thrombosis that occurs either by direct contact activation on the device surface (device thrombosis) or indirectly as a result of cardiac thromboembolism provoked by changed hemodynamics and flow characteristics after device implantation (device-related thrombosis (DRT)). In the following review, we shall briefly discuss the mechanisms of device thrombosis and DRT and give an overview of the clinical problems, epidemiological evidence and management strategies of cardiac device thrombosis. A separate paragraph will provide an update about the mechanisms of left ventricular assist device (LVAD) thrombosis and give guidance on treatment strategies.

Mechanisms of device thrombosis

Implantable devices usually contain a prothrombotic surface that lead to activation of the coagulation system by a complex interplay between blood cells and plasma proteins. This process is characterized by enhanced adsorption of proteins, adhesion of platelets, leukocytes, and red blood cells, activation of the extrinsic coagulation cascade leading to thrombin generation, and activation of the complement system. Thrombogenicity is further enhanced by the underlying cardiac disease, particularly heart failure, leading to disturbances in endothelial function and impaired blood flow and composition. Protein adsorption is caused by negatively-charged hydrophilic surfaces that acts independently from blood flow velocity.(1) Fibrinogen, fibronectin and von Willebrand factor (vWF) primarily adhere to the surface of devices and lead to activation and adhesion of platelets. Negatively charged surfaces further activate factor XII to factor XIIa

thus initiating the intrinsic pathway. Factor XIIa also induces complement activation leading to thrombin amplification. Leukocytes, in particular neutrophils, also adhere to fibrinogen immobilized on the device surface via CD11b/CD18 (Macrophage-1 antigen 1 (MAC-1)).(2) Following adhesion and activation, platelets interact with leucocytes mainly via cross-linking of P-Selectin with P-Selectin glycoprotein ligand-1 (PSGL-1) and MAC-1 with glycoprotein 1b alpha (GP1bα). Leucocyte degranulation contributes to a prothrombotic and proinflammatory milieu by generating free radicals, releasing interleukins and tumor necrosis factor alpha (TNFα) and activating monocytes, leading to induction of tissue factor expression and consequent initiation of the coagulation cascade (Figure 1). Attempts to reduce protein adsorption on the device surface have been mainly driven by the reduction of electrostatic and hydrophobic interactions between plasma proteins and the artificial surface. Synthetic and natural materials that hamper this process include polyethylene oxide, phosphorylcholine, pyrolytic carbon, albumin, and elastin-inspired protein polymers.(1)

Methods

We performed a systematic search regarding device thrombosis and DRT and antithrombotic management after cardiac device therapy in the international guidelines, including the guidelines and position papers of the European Society of Cardiology (ESC) (3,4) and the American Heart Association (AHA)/American Stroke Association (ASA).

In addition, we searched for relevant ongoing clinical trials in the registry of clinical trials (clinicaltrials.gov) using keywords “Mitral interventions”, “LAA occlusion”, “antithrombotic treatment”, “patent foramen ovale / PFO”. A review of current literature was performed using the

search terms “device related thrombosis”, “antithrombotic therapy after cardiac devices”, “thrombolytic therapy for device thrombosis”, “patent foramen ovale / PFO”, “cardiac occluder”, “left atrial appendage (LAA) occlusion”, “Amplatzer Cardiac Plug and thrombosis”, “Amplatzer Amulet and thrombosis”, “Watchman and thrombosis”, “pacemaker related thrombosis”, “ICD related thrombosis” and “LVAD thrombosis” in pubmed.gov.

Risk factors for patent foramen ovale (PFO) closure device thrombosis

Indications for PFO occluders have recently increased in patients with cryptogenic stroke / ESUS and PFO after positive randomized outcome studies.(5–7) The most investigated devices in larger clinical trials are the AMPLATZER and the GORE occluders. Currently, expert opinions favor implantation of a PFO occluder after cryptogenic stroke in younger patients (i.e. patients younger than 60) and patients with moderate-to-large atrial shunt. In particular, there is a stronger recommendation regarding PFO closure compared to antiplatelet therapy.(4) To date, there is lack of data regarding the benefits of PFO occluder compared to anticoagulant therapy.(8) Stroke rates in PFO trials were in the range of 0 to 5% depending on the device and the time of follow-up and usually lower compared to the medical arm in recent trials.(5–7,9) It is difficult to determine association with device thrombosis as, in some studies, different occluder devices were used (7) and systematic TOE follow-up was performed in only few trials. Of note, there have been observations that stroke occurred even if there was no detection of device thrombosis nor device leakage (10,11), highlighting the importance of careful risk assessment to first clarify the causality of paradoxical embolism and second defining the residual stroke risk after PFO occluder.

PFO closure device thrombosis is a rare event and has been described in ranges from 0.4 to 1.2% depending on type of occluder and duration of follow-up. (Figure 2, (12,13)). In a systematic series of 620 patients treated with the AMPLATZER PFO occluder for secondary prevention of paradoxical embolism, 6-month follow-up revealed only two cases showing small thrombi on the atrial disk.(14) Whereas thrombi at the right atrial disc have been usually reported, there are single reports of organized thrombi at the left atrial disc (example of echocardiographic finding in Figure 3C and (15)). It is matter of debate whether PFO occluder thrombosis is related to the device itself or rather due to a hypercoagulable state as a consequence of alteration in hemodynamics and endothelial function. Importantly, unrecognized venous thrombosis leading to paradoxical thromboembolism might have preceded the cerebrovascular event and thus may impact the risk for recurrent venous thromboembolism (VTE) and device thrombosis if not adequately treated by anticoagulation after PFO occlusion.

Antithrombotic treatment after PFO closure and treatment strategies to resolve device thrombosis

Usually, dual antiplatelet therapy (DAPT) is recommended after PFO occluder insertion. The appropriate duration of DAPT is unknown and varied in clinical trials and registries for investigation of specific devices. The duration and dosing of antiplatelet therapy patients was 81 to 325 mg of aspirin plus clopidogrel daily for 1 month, followed by aspirin monotherapy for 5 months in the RESPECT trial.(5) Current expert opinions give the recommendation of one to six months dual antiplatelet therapy after PFO occlusion followed by antiplatelet monotherapy for at least 5 years.(4) There is still some uncertainty about the causal relationship between PFO occlusion and new onset of atrial fibrillation (AFIB). In a meta-analysis included in the latest ESC

position paper on PFO (4), the detection rate of new-onset AFIB was similar with the AMPLATZER PFO occluder whereas it was more frequent for the GORE CARDIOFORM device when compared with medical therapy, respectively. In another metaanalysis, device-associated AFIB, in most cases, occurred within 45 days after implantation, was often transient with low recurrence and was seldom associated with strokes.(16)

The risk of thromboembolic stroke in device-induced AFIB is unknown and there is currently no consensus about risk stratification, post-implantation diagnostic work-up for AFIB detection and the therapeutic consequences. In contemporary patient cohorts treated with PFO occluder (usually younger than 65 years, with no relevant vascular risk factors), the AFIB associated stroke risk is probable of minor relevance. However, systematic trials should further address this issue and investigate the clinical relevance of device associated AFIB depending on clinical risk and AFIB burden/duration of episodes. A proposed algorithm of short-term (e.g. 1-3 months) versus long-term (indefinite) anticoagulation depending on onset of AFIB (≤45 days versus >45 days after implantation) has been proposed by Elgendy et al.(16)

Anticoagulation using vitamin K antagonists (VKA) with tight INR control (~3.0) has been shown to resolve thrombus attached to the surface of the PFO occluder in single case reports.(14,17) In patients with large thrombus mass and high risk of ischemic stroke, thrombolytics and GP IIb/IIIa receptor blockers have been suggested as an effective and safe therapy according to single-case experiences.(18)

Risk factors for left atrial appendage (LAA) closure device thrombosis

A number of LAA occluder (LAAO) devices have been developed including the WATCHMAN (Boston Scientific), the AMPLATZER Cardiac Plug™ and the second generation AMPLATZER Amulet™ LAA occluder (Abbott). The Lariat system is an extracardiac interventional device and therefore not part of this focused article on endocardiac devices. Most experience from randomized and/or post-marketing registries exists for the WATCHMAN and AMPLATZER LAAO device. Therefore reliable rates of device thrombosis incidence can be currently provided for these two devices, only. In contrast to PFO occluder thrombosis, thrombosis on LAA closure devices is more common and has been reported in up to 17%.((19); Table 1). In the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) study, DRT was observed in 4.2% after initially-successful implantation of the WATCHMAN occluder (20). In a pooled analysis of the major trials and registry for the WATCHMAN device, including the PROTECT-AF, PREVAIL (Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), CAP (Continued Access to PROTECT AF registry) and CAP2 (Continued Access to PREVAIL registry) the incidence of DRT was 3.7% and it was associated with a higher rate of stroke and systemic embolism.(21) In a CT-follow-up study including 117 patients with both WATCHMAN and AMPLATZER (Cardiac Plug and Amulet) the DRT prevalence was 16% at 3 months after implantation.(22) There have been reports on early and late occurrence of LAAO thrombosis. In a recent systematic registry, early (within 1.5 months), late (between 1.5 and 6 months) and very late (between 6 and 12 months) LAAO thrombosis occurred in 28.6%, 28.6% and 42.9% of the cases, respectively.(23) In the latter study, the incidence of DRT was not associated with duration of DAPT but rather with patient-related risk factors. Different risk factors have been proposed including device type or positioning, LAA anatomy, post-procedural antithrombotic regimen and clinical risk factors. In a systematic

echocardiographic evaluation, thrombi were predominantly observed within the untrabeculated region of the LAA ostium between the left upper pulmonary vein ridge and the occluder disc. The investigators therefore suggested suboptimal LAA occlusion as the main reason for thrombus formation.(24) There have been reports on other locations of the thrombus on the occluder disc (in case of the AMPLATZER occluder, Figure 3A+B) or on the polyethylene terephthalate (PET) fabric of the WATCHMAN device.(25) A recent registry identified older age and history of stroke as predictors of thrombus formation, whereas DAPT and oral anticoagulation at discharge were protective factors. Thrombus on the device was independently associated with ischemic strokes and transient ischemic attacks (TIAs) during follow-up.(26) Another case-control study in patients treated with the AMPLATZER LAAO found an association between DRT with incomplete coverage of the limbus by the Amulet disk, a lower left ventricular ejection fraction, larger LA diameter, greater spontaneous echocardiogram contrast, and lower peak LAA emptying velocity as compared to patients without DRT.(24) AFIB burden has also been discussed as a potential risk for LAAO DRT.(21) Clopidogrel non-responsiveness measured by platelet function testing has been associated with DRT in one study (27) and showed an association with bleeding events and not with DRT after LAAO implantation in another cohort study.(28)

1 Table 1: Reported incidence of LAAO thrombosis

Study/ Reference	Device	Number of patients	Reported rate of LAA occluder thrombosis (imaging modality)	Reported antithrombotic therapy before thrombus detection	Outcome
(23)	WATCHMAN, AMPLATZER Cardiac Plug	N=43 WATCHMAN, N=59 AMPLATZER	7.1 % after 12 months (70% TOE/ 30 % CT)	DAPT	Association of DRT with stroke
(26)	WATCHMAN, AMPLATZER	N=272 WATCHMAN devices and 197 AMPLATZER devices	7.2% per year (77.5 % TOE, 22.5% CT)	No OAC, no APT 7.7%; Single APT 35.8%; Dual APT 23.0%; OAC, no APP 28.9%; OAC plus APT 4.6%	DRT independent predictor of ischemic strokes and TIA
ASAP (29)	WATCHMAN	N=150	4% at a mean follow-up of 14.4 months (TOE only)	6 months of a thienopyridine antiplatelet agent (clopidogrel or ticlopidine) and lifelong aspirin	Only 1 out of 6 DRT was associated with a stroke (341 days post-implant)
PROTECT-AF (20)	WATCHMAN	N=269	4.2% (TOE only)	45-day OAC followed by APT	Not reported
(22)	WATCHMAN and AMPLATZER (Cardiac Plug and Amulet)	N=117 (n=34 WATCHMAN, n=93 AMULET)	16% after 3 months (CT only)	Not reported	No association with stroke nor TIA
(30)	AMPLATZER Cardiac Plug	N=339 with available TOE	3.2% at a median of 134 days (TOE FU) and median of 355 days for clinical FU	62.4% DAPT, 31% SAPT, 6.2 % OAC, 0.4 % No therapy	No association with stroke
(24)	AMPLATZER Amulet	N=24	16.7% (TOE)	3-month DAPT	Not reported
(31)	AMPLATZER Cardiac Plug	N=198 patients with previous ICB	1.7% (TOE)	74.5% with ASA monotherapy	Not reported
(32)	AMPLATZER Cardiac Plug	N=1,047	4.4% after median of 7 months (TOE avalaible in 63% of patients)	Aspirin monotherapy in one third of patients	No impact on stroke rates

2

Antithrombotic treatment after LAA closure and treatment of LAAO DRT

There are currently no randomized trials comparing the efficacy and safety of different antithrombotic regimens in patients undergoing LAA closure. In contrast to randomized clinical trials, patients with AFIB in real-world practice are usually selected for interventional LAA closure if anticoagulation is not tolerated due to enhanced bleeding risk.(33) Previous data on the efficacy and safety of LAAO followed by either short-term anticoagulation and subsequent antiplatelet therapy or antiplatelet therapy from the beginning has been mainly compared to VKA alone in patients without LAAO. According to current expert opinions, dual antiplatelet therapy for 3 to 6 months followed by aspirin monotherapy after LAAO is recommended; however, the evidence for efficacy and safety of this regimen is sparse and the antithrombotic therapy in clinical trials leading to device approval was heterogeneous. In the PROTECT-trial, antithrombotic strategy after implantation of the WATCHMAN was 45-days of warfarin therapy followed by DAPT. In a recent registry including 1,047 patients who received the AMPLATZER LAAO, aspirin monotherapy was the most common strategy without major adverse impact on thromboembolic event rates.(32) In light of lacking guidance real-world antithrombotic regimens are very heterogeneous among international centers according to a recent survey by the European Heart Rhythm Association (EHRA) ((34), Figure 4). The efficacy and safety of occluding the LAA compared to medical therapy is a matter of investigation in a number of ongoing trials. Several trials are currently testing the superiority of endocardial LAAO followed by antiplatelet therapy compared to best medical care, including non-vitamin K-antagonists (NOAC) therapy in patients with atrial fibrillation (CLOSURE-AF, clinicaltrials.gov NCT03463317, PRAGUE-17, clinicaltrials.gov NCT02426944, OCCLUSION-AF, clinicaltrials.gov NCT03642509). Since leakage and incomplete coverage was found to be one of the predictors for thrombus formation, consecutive closure of leakage using another LAAO was reported as potential strategy after thrombus resolution following

anticoagulation in one case.(35) Given the information on DRT incidence, a more personalized antithrombotic regimen in the post-procedural phase might be reasonable, i.e. treating patients with risk factors for DRT such as reduced left ventricular ejection fraction, larger LA, high CHA_2DS_2VASc score, or incomplete sealing of the device with a short course of an oral anticoagulant followed by antiplatelet therapy. Only sparse information exists with regard to treatment of LAAO related thrombosis. In the EHRA survey, the most common practice after LAAO DRT was low molecular weight heparin followed by NOAC treatment.(34) Anticoagulation intensity and duration after device thrombosis is challenging as by indication this population represents a high bleeding risk population. In most patients thrombolytic therapy is contraindicated. In a small series of cases, 6-month VKA treatment in combination with aspirin led to a resolution of thrombi in all patients without adverse bleeding events.(25). In another small series of DRT, NOACs were able to resolve thrombi in all patients after a mean of 6 ±2 weeks.(24) Although not reported for the treatment of LAAO thrombosis, an interventional retrieval of large thrombotic masses under cerebral protection might represent a bail-out strategy in selected patients with high surgical risk and contraindication against thrombolytic therapy as proven in a recent case of a large left atrial thrombus mass.(36)

Risk factors for thrombosis after mitral interventions and transcatheter mitral valve implantation

Transcatheter mitral-valve repair with the MitraClip device has been increasingly applied in patients with mitral regurgitation (MR) due to degenerative mitral valve disease. In patients with functional MR, careful patient selection is essential as recent randomized trials have shown conflicting results. The MitraFR trial showed no benefit (37) whereas a mortality reduction was

demonstrated in the latest Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial (38) in different functional MR / heart failure populations. Heart failure per se is associated with increased risk for thromboembolism and stroke. (39) Altered hemodynamics, impaired endothelial function and different blood composition, all included in the Virchow triad, are associated with increased thrombogenicity in heart failure. There are currently no systematic analyses from large clinical trials focusing on thrombus occurrence after the MitraClip procedure. Annual stroke risk has been reported in 2/184 (1.1%), 6/567 (1.1%), 9/423 (2.1%) in the EVEREST II trial (n = 184), ACCESS-EU registry and in the TRAMI (40) respectively taking into consideration that not all cardiac thrombi must become clinically apparent and not all strokes are of cardioembolic nature or are device-related in this particular patient population. In the latest COAPT trial stroke occurred in 11/302 (4.4%) after 24 months in the device arm and was not significantly different from the stroke rate in the control group (38). A number of cases have been reported showing early thrombosis associated with the MitraClip procedure. In these cases, new thrombus formation either occurred adherent to the MitraClip or the delivery system (41,42), in the left atrium (43) in the left atrial appendage (LAA) (44) or left ventricle (45). In addition, thrombus formation might also occur on the transseptal sheath as was reported previously in up to 9% of patients despite adequate periprocedural anticoagulation.(46) It was recently suggested by one case report that altered hemodynamics may enhance thrombogenicity in the left atrium which can be measured by thrombelastography in blood taken from the left atrium during the procedure (Figure 5, with permission). These observations have not yet been confirmed in larger series of patients undergoing the MitraClip procedure.

Recently, transcatheter mitral valve replacement (TMVR) has emerged as treatment option in high risk surgical patients by using TAVR devices (e.g. Sapien XT/3, Edwards) in mitral position in

patients with previous mitral valve prosthesis or calcified mitral disease. In addition, novel TMVR devices are currently tested for clinical use in feasibility trials (CardiAQ ™, Edwards; Fortis ™, Edwards; Tiara™, Neovasc; Tendyne ™, Abbott; Intrepid™, Medtronic; HighLife ™, Highlife Medical). There are few small cohort studies suggesting higher prosthetic valve thrombosis rates (~15%) after TAVR devices in mitral position compared with those in aortic position (47,48). These high rates are potentially related to low flow conditions in mitral disease. Currently, there is sparse information about the risk of valve thrombosis after TMVR with novel mitral prosthetic devices. The TMVR program with the Fortis valve was prematurely halted due to cases of valve thrombosis (49). In the Tendyne Feasibility study, prosthetic leaflet thrombosis was detected in 1 of 30 patients at follow-up, which resolved after increased oral anticoagulation with warfarin.(50)

Antithrombotic treatment and strategies to prevent thromboembolism after mitral interventions and transcatheter mitral valve implantation

Effective periprocedural anticoagulation usually by unfractionated heparin is essential to prevent thrombus formation in the left atrium. The application of cerebral protection devices has been shown to be feasible in a small series of patients and might be beneficial in selected patients at high thrombotic risk (e.g. low flow in LAA, spontaneous echo contrast in LAA).(51) Long-term antithrombotic treatment after mitral interventions is empiric. By nature, there is a higher prevalence of AFIB in patients with mitral disease and therefore many patients require long-term anticoagulation if the bleeding risk permits. NOACs in guideline recommended doses investigated in AFIB trial might be a better choice for these often elderly patients exhibiting higher risk for major and intracranial bleeding. However, there are no studies comparing different anticoagulant strategies including NOACs in AFIB patients undergoing MitraClip. Current empiric treatment is

dual antiplatelet therapy in patients undergoing the MitraClip procedure who have no AFIB. In a recent monocentre registry, involving 254 patients with sinus rhythm undergoing percutaneous mitral intervention, the combination of apixaban and aspirin for 4 weeks followed by antiplatelet therapy alone was associated with a lower rate of the combined endpoint of all-cause mortality, all stroke and rehospitalization for congestive HF or MI compared to single (72%) or dual (28%) antiplatelet therapy only (1.4% vs. 7.6%; P = .02). There was a non-significant trend towards lower stroke rate in the apixaban plus aspirin group. Bleeding events at 30 days were low and not significantly different between the groups.(52) Combination therapy with an oral anticoagulant and one antiplatelet agent has been frequently applied in AFIB patients (53), however there is no clinical trial evidence including the use of NOACS in this patient population. Short-term (30-day) anticoagulation (Coumadin with an INR 2.0-3.0) regardless of AFIB has been suggested to reduce stroke risk without increasing bleeding after the MitraClip procedure.(54)

It is reasonable to adopt the recommendation of at least 3 months anticoagulation after surgical mitral bioprostethis to TMVR.(3,55) There is lack of evidence whether even prolonged anticoagulation or combination with antiplatelet therapy is beneficial in this seeting. It is our opinion, that in patients undergoing TVMR, OAC combined with single antiplatelet should be considered due to the higher risk of prosthetic hear valve thrombosis regardless of the presence of AFIB on a case-by-case basis depending on the individual bleeding risk.

Risk factors for pacemaker / implantable cardioverter-defibrillator (ICD) lead thrombosis

Following the adoption of high-resolution echocardiography and intracardiac echocardiography, thrombotic coverage of pacemaker and ICD leads has been increasingly recognized (Figure 3D). In a retrospective study of 71,888 echocardiographic studies of patients with pacemaker leads and no diagnosis of endocarditis, thrombotic alterations were found in 1.4% of patients.(56) With TOE

and intracardiac echocardiography (ICE) the rate was even higher. In a recent study of pacemaker patients undergoing ablation the rate of lead thrombosis was 30% by using ICE.(57) In the majority of patients, these thrombotic lesions were not detected by conventional transthoracic echocardiography. Locations of thrombotic lesions were reported both on ventricular and atrial leads (Figure 3D). The presence of thrombi was significantly associated with higher pulmonary artery systolic pressure.(57) In some cases the differentiation between lead thrombosis and device-related infective-endocarditis is challenging or not possible. A single report suggested snare retrieval of the mass as a diagnostic and therapeutic option.(58) Technical demand and safety of this procedure is a major issue. A case-control study suggested that the risk of thrombosis, including lead thrombosis after pacemaker insertion, is not associated with technical parameters of leads or implantation technique but rather patient-related established risk factors for VTE.(59)

Antithrombotic treatment after pacemaker / ICD lead thrombosis

There is no specific recommendation regarding the antithrombotic therapy after pacemaker insertion besides the antithrombotic therapy that is defined by patients´ risk factors and the underlying cardiovascular disease. Many patients requiring pacemaker or ICD therapy have concomitant coronary artery disease (CAD) or AFIB and thus the antithrombotic regimen is very heterogeneous.(60) In patients already pre-treated with NOACs, pacemaker insertion can be performed without stopping the anticoagulant to reduce the thrombotic risk in the early postprocedural phase.(61) The optimal therapy of pacemaker lead-associated thrombosis has been controversially discussed. The treatment decision is generally determined by the size and mobility of the thrombotic mass and accordingly the risk of fatal pulmonary embolism, or paradoxical embolism in the case of intracardiac shunt. Treatment options described in the literature encompass anticoagulation with VKA and thrombolysis with fibrinolytics including streptokinase, urokinase

and recombinant tissue plasminogen activator.(58–62)

. VKA after initial heparin treatment was effective with regard to thrombus resolution in pacemaker-related upper extremity deep vein thrombosis.(67) Open heart surgery has been the most commonly employed treatment option when dealing with relatively large thrombi or in cases of unsuccessful lysis. Interventional removal in high-risk surgical patients has been applied with single-experience.(58)

Risk factors for thrombosis of cardiac assist devices

Extracorporal life support, Impella

Extracorporal life support (ECSL) using extracorporal membrane oxygentation (ECMO) is associated with disturbances in coagulation. Both, use of venovenous (VV) and venoarterial (VA) ECMO has increased over the last decade. On the one hand enhanced bleeding is observed in long-term recipients of ECLS. This is mainly due consumption of coagulation factors in particular Factor VIII, consumption of platelets by activation and due to shear-induced modulation of vWF multimers. On the other hand, ECMO provides a large artificial surface, which stimulates pro-coagulatory and pro-inflammatory processes. Different components have been identified to influence platelet activating and pro-coagulatory processes at various levels. In artificial models, the pump carried the highest risk for platelet activation, followed by the reinfusion cannula and the connector.(68)

In addition, hypothermia often applied in cardiogenic shock patients undergoing ECLS leads to platelet activation and enhanced thrombotic risk.

Thrombotic complications with the ventricular assist Impella device (2.5, CP, 5.0, RP, Abiomed). have been described in only few cases and were mostly associated with left-ventricular (LV)

thrombosis due to poor ventricular function / LV aneurysm. Implantation of the Impella is contraindicated in patients with pre-existing ventricular thrombus.

Left ventricular assist devices (LVAD)

LVAD are increasingly used due to increasing numbers of potential recipients, shortage of suitable donors and development of better devices. LVADs can be used as bridge to recovery, bridge to transplant, bridge to destination, or bridge to candidacy.(69,70) Currently, the most commonly-used device is a continuous-flow LVAD (CF-LVAD), either as axial-flow pump or as a centrifugal-flow pump. CF-LVADs are currently the preferred option as these are superior in terms of durability, less surgical complications, energy efficiency, and thrombogenicity.(71) Despite the evolving technology of the devices and better understanding of their indications, complications of device therapy are still common and associated with increased morbidity and mortality. Typical complications are: bleeding, infections, and LVAD thrombosis.(39,40) LVAD thrombosis is a life-threating complication that may lead to hemodynamic deterioration, embolic events and the need of high-risk therapeutic procedures and is reported in 1.4% to 11.8% of cases.(68–71)

Data from the INTERMACS registry suggested higher DRT rates with the HeartMate II compared with its predecessor. LVAD thrombosis occurred in up to 8.4% in a recent registry in patients with the HeartMate II. In the same study, median time from implantation to thrombosis was 18.6 months.(75) Improved implant techniques and consistent post-operative management may further reduce DRT as shown in another large pooled analysis.(76) Technical advances leading to the latest generation magnetically-levitated HeartMate III significantly reduced the rate of pump thrombosis. This new miniaturized centrifugal-flow pump is designed to enhance hemocompatibility by minimizing shear force effects on blood components. In the MOMENTUM 3 trial, suspected events of pump thrombosis occurred in 1.1% of recipients of HeartMate III centrifugal pump compared

to 15.7% of the patients who received the axial-flow pump group (hazard ratio, 0.06; 95% CI, 0.01 to 0.26; P<0.001).(77)

The mechanisms and pathophysiology behind LVAD associated thrombosis are complex and a subject of ongoing research. Risk factors are internal high shear stress, device material and surface characteristics, chronic infection, and inadequate anticoagulation or malposition of the device. Moreover, there are also patient-dependent (pre-existing ventricular and/or atrial thrombus, non-compliance hypercoagulation disorders, blood pressure management) risk factors. The diagnosis of LVAD thrombosis is complex and needs an interdisciplinary team with experience. Goldstein et al. established an algorithm for suspected LVAD-thrombosis and management, which has been well accepted in the community of experts in mechanical circulatory support (Figure 7).(78). In most cases LVAD thrombosis is diagnosed by clinical assessment including laboratory findings combined with changes in the LVAD values (power consumption, speed, and estimated flow).

Management of left ventricular assist device thrombosis

When the diagnosis of CF-LVAD thrombosis is clear there are surgical therapeutic options, such as LVAD exchange and non-surgical options, including thrombolytic and antithrombotic therapies (i.e. direct thrombin inhibitor, tissue plasminogen activator, or glycoprotein IIb/IIIa antagonist).(76–80)

To avoid emergency major surgery (pump exchange), which is associated with morbidity and mortality the concept of direct thrombolytic therapy (tPA) has been performed successfully for many years.(84) However, the medical intervention carries the risk of not knowing whether the thrombus is fully resolved or simply reduced. Based on this assumption, some authors observed an increased risk for recurrence of LVAD-thrombosis three times greater in those who experienced

initial surgery.(85) It is well known that after successful thrombolytic therapy high rates of bleeding complications and hemorrhage strokes have been observed.(86) In a recent meta-analysis by Luc et al. involving 43 individual trials, it has been shown that surgical pump exchange is superior to medical therapy with a higher success rate of pump thrombosis resolution, lower mortality, and lower recurrence rate.(17) Especially for the newer (intrapericardial implanted) generation of LVADs, it seems to be that the risk of complications is even lower, as the surgical approach is less traumatic if performing the exchange without sternotomy. Even repetitive LVAD exchanges can be done with an accepted risk via the minimally-invasive approach. (87) Also, the surgical therapeutic option gives the opportunity to upgrade the current LVAD to the newest available generation, because there still numerous patients on the 2nd generation of LVADs. (88)

Periprocedural antithrombotic regimen during cardiac device therapy in patients pretreated with or naïve to antithrombotic therapy

Usually, interruption of antithrombotic therapy should be kept as short as possible in high risk patients having a clear indiciation for antiplatelet or anticoagulant treatment (e.g. within 6 months of DAPT after PCI or in AFIB patients with high stroke risk receiving OAC). Pacemaker implantation should be performed under continued antithrombotic therapy unless patient is at very high perioperative bleeding risk according to results of recent RCTs and guideline recommendation.(61,89,90) There are currently no systematic protocols regarding periprocedual anticoagulation and bridging regimens in patients undergoing structural heart interventions. Interventions presented here (PFO-occlusion, LAAO, MitraClip) can be performed under continued antiplatelet therapy if applicable. Temporary cessation of anticoagulant therapy should be handled on a case by case basis considering the individual thrombotic and bleeding risk. It is

sufficient to pause the NOAC on the day of the procedure with once daily dosing regimens and in the evening before with twice daily regimens. However, there might be situations where a continuous anticoagulatory effect is desirable. For instance, a patient undergoing MitraClip with high degree of spontaneous echo contrast in preprocedural TOE would benefit from a continuous OAC or bridging with heparin to avoid left atrial/LAA thrombus formation during the procedure. With regard to IFU and guideline recommendations, intraprocedural ACT using UFH should be 250 to 300 s for LAAO, at least 200 s for PFO/ASD closure and 250 to 300 for MitraClip.(91) OAC should be reinitiated at earliest convenience depending on the postinterventional bleeding risk. Temporary low heparinization might be applicable to prevent periprocedural thrombotic events while avoiding access site bleeding risk. Loading with clopidogrel (300 to 600mg) should take place prior to procedure for LAAO, the day before PFO occlusion and directly after MitraClip according to protocols and clinical trials and IFUs.(7,92,93; Figure 6) Systematic trials investigating the extent and the timing of periprocedural antiplatelet therapy are lacking.

Management of periprocedural antithrombotic therapy in cardiac assist device therapy

Extracorporal life support, Impella

Attempts have been made to decrease contact activation by the artificial surface by using biocompatible coatings and less thrombogenic hollow fiber membranes.

During ECSL, heparinization aiming at an activated clotting time (ACT) of 180 to 220 is mandatory, however, clinical scenarious in these critically ill patients sometimes require modifcations of these target values.

There is currently no consensus how to control exaggerated platelet consumption under ECLS. After careful exclusion of heparin induced thrombocytopenia (HIT), pharmacological platelet inhibition with short acting compounds (e.g. iv. $P2Y_{12}$ inhibitor cangrelor) have been used in some case reports showing favourable outcome (94), while bleeding was still frequent (95). In an animal model and *in-vitro* model of extracorporal circulation (Chandler-loop), administration of cangrelor led to a significant decrease of platelet activation and increase of platelet count under hypothermia.(96)

Pro- and anticoagulatory processes clearly correlate with shear forces and duration of ECLS. Therefore, duration should be restricted if possible and dedicated protocols regarding pump flow settings, including cardiac decompression (97), timing of exchange of the oxygenator or the entire circuit, surgical interventions in case of cardiac thrombosis and haemostaseologic monitoring should be integrated to early detect and counteract thrombotic alterations.

There are no standardized anticoagulation protocols in patients treated with Impella. Heparinzation with an ACT of 160-180 seconds is recommended by the manucfacturer. A recent case series of cardiogenic shock patients receiving the Impella CP device showed that aiming at anti factor Xa levels between 0.1 and 0.3 U/ml were associated with low thrombotic events rates.(98)

LVAD

During LVAD surgery with cardiopulmonary bypass a full anticoagulation is recommended comparable with other cardiac surgery procedures with cardiopulmonary bypass. At the end of surgery a full reversal and restoration of all blood components should be achieved. The dose of heparin used to prevent blood clotting during cardiopulmonary bypass should be around 300–400

U kg−1 plus additional doses to achieve and maintain an activated clotting time (ACT) of greater than 450 s, if necessary a usage of a heparin dose response (HDR) technique might be helpful.(99,100)

Postoperatively, anticoagulation with heparin is recommended to begin once chest tube output has significantly decreased. Initially, the target activated partial thromboplastin time is 40 s; it is progressively increased to 55–60 s within the first 48–72 h after surgery. Accompanying to unfractionated heparin administration the oral anticoagulation with vitamin k antagonist should be started once the clinical condition is stable and oral intake is feasible. The INR (the international normalized ratio) target should between 2.0 and 3.5 according to device company recommendations for modern LVADs. However there is inconsistency in the literature whether antiplatelet therapy is required and what the dose of therapy should be administered. Recently, a systematic review has shown that most centers starting aspirin 24 to 72 hours postoperatively without any complications.(101)

Limitations of current evidence and future directions

Although a growing number of patients experience multiple device therapies either simultaneously or in staged procedures during the course of cardiac disease (e.g. Mitraclip and LAA occlusion, Mitraclip/ASD closure, Mitraclip and devices for cardiac resynchronization), there is limited evidence how these multiple interventions influence thrombotic risk. This might require specific clinical attention and tailored antithrombotic strategies might become necessary in these patients. Systematic studies are still warranted to test different antithrombotic drugs focusing on combination therapy and duration of treatment and the current evidence is mainly based on case

reports, case series and observational studies. In addition, decision algorithms need to be developed and applied to predict thrombotic and bleeding risk. This will enable careful selection of patients who benefit from cardiac prostheses or who might be better treated with best medical care or non prosthetic implant methods like the NobleStitch™ for PFO or the Lariat™ for LAA occlusion. Current biomaterial research focusses on synthesizing less thrombogenic biomaterials. Innovative techniques in tissue engineering, application of stem cell technology and coating with biologically active, antithrombotic compounds (e.g. PEG-CTI coated surfaces) in valve and device development might help to improve bioavailability and help to avoid the need for for systemic antithrombotic therapy. Finally, novel strategies of antithrombotic treatment like factor XI/XIa, XII/XII inhibition using small molecule inhibitors, antibodies or antisense oligonucleotidea are currently in the pipeline representing attractive strategies to inhibit the contact activation pathway on artificial devices.(1,102,103)

Conclusions

With the incremental use of cardiac devices, there is clinical need to better define the individual risk for thromboembolic events after implantation and thrombotic alterations on the device itself. As in some patients (e.g. patients with indications for LAAO), there is a concomitant high bleeding risk and careful tailored therapy is necessary to navigate between Scylla and Charybdis. Device thrombosis should be avoided as it is usually associated with increased risk for stroke and systemic thromboembolism, as well as bleeding in case of intensified antithrombotic management. Risk estimation starts with a careful selection of patients who benefit from device therapy. Regarding PFO and LAA occluders, ongoing and future trials will have to show whether device therapy can compete against best individual antithrombotic therapy including NOACs. A proposed algorithm based on current knowledge and treatment practice of device specific antithrombotic therapy and

management of DRT is given in Figure 6. LVAD thrombosis represents a serious event limiting prognosis in end-stage heart failure patients and strategies for early detection and optimal management are of utmost importance (Figure 7). Although with newer generation assist devices (e.g. LVAD 3rd generation continuous flow devices) the reported incidence of device thrombosis could be reduced, application in real-world heart failure patients will have to confirm whether these results can be translated from controlled randomized trials with highly selected patients.

Figure legends

Figure 1: Mechanism of contact activation on artificial surface leading to device thrombosis (Figure was composed by using Adobe Stock vectors)

Figure 2: Reported locations and frequencies of device related thrombosis after implantation of endocardiac devices.

Figure 3: A) 2D TOE images and B) 3D TOE images of DRT 6 weeks after LAA occluder (Amplatzer Cardiac Plug) in a 70 year old patient C) DRT 3.5 months after PFO occluder implantation in a 68 year old patient; D) Pacemaker associated thrombosis on atrial lead in a patient with sick-sinus-syndrome.

Figure 4: Predominant oral antithrombotic protocols (percentage) in the long-term phase (> 6 months) post endocardial LAAO implantation in patients without contraindications to VKA or NOAC and no leak during follow-up TOE (A), in patients with absolute contraindications to VKA or NOAC and LAA leak > 5mm (B) or device thrombus (C) during follow-up transoesophageal echocardiography; according to EHRA survey among 33 European centres, modified according to (34)

Figure 5: Case of LAA thrombosis shortly after MitraClip implantation due to altered hemodynamics and increased thrombogenicity measured by thrombelastography (according to (44) permission obtained)

Figure 6: Proposed algorithm for antithrombotic therapy based on risk stratification following cardiac device therapy.

Figure 7: Proposed algorithm for diagnosis and management of LVAD thrombosis (according to (78) permission obtained)

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What does this paper add?

This paper summarizes the current evidence, efficacy and safety of current antithrombotic treatment, discusses risk factors and suggests treatment algorithms of device-related thrombosis including PFO- and LAA-occluder, MitraClip/TMVR, pacemaker lead and left ventricular assist device thrombosis.

What is known about this topic?

With growing implantation rates, the clinical problem of device-related thrombosis increases and identification of risk factors and individualized antithrombotic treatment patterns are warranted.