Thrombogenicity and Antithrombotic Strategies in Structural Heart Interventions and Nonaortic Cardiac Device Therapy—Current Evidence and Practice

Tobias Geisler¹ Rezo Jorbenadze¹ Aron-Frederik Popov² Karin L. Mueller¹ Dominik Rath¹
 Michal Droppa¹ Juergen Schreieck¹ Peter Seizer¹ Robert F. Storey³ Steen D. Kristensen⁴
 Andrea Rubboli⁵ Diana Gorog^{6,7} Daniel Aradi^{8,9} Dirk Sibbing^{10,11} Kurt Huber^{12,13}
 Meinrad Gawaz¹ Jur Ten Berg¹⁴

¹ Department of Cardiology and Angiology, University Hospital, Eberhard-Karls University of Tübingen, Tübingen, Germany

² Department of Thoracic and Cardiovascular Surgery, University Medical Center Tübingen, Eberhard-Karls University of Tübingen, Tübingen, Germany

³ Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom

⁴ Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

⁵ Division of Cardiology, Department of Cardiovascular Disease—AUSL Romagna, Ospedale S. Maria delle Croci, Ravenna, Italy

⁶ National Heart and Lung Institute, Imperial College London, London, United Kingdom

⁷ University of Hertfordshire, Hertfordshire, United Kingdom

⁸ Heart Center Balatonfüred, Balatonfüred, Hungary

⁹ Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Address for correspondence Tobias Geisler, MD, MHBA, Department of Cardiology and Angiology, University Hospital, Eberhard-Karls University of Tübingen, Tübingen, Germany
 (e-mail: tobias.geisler@med.uni-tuebingen.de; togeisler@web.de).

¹⁰ Department of Cardiology, LMU München, Munich, Germany

¹¹ DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

¹² 3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminenhospital, Vienna, Austria

¹³ Medical Faculty, Sigmund Freud University, Vienna, Austria

¹⁴ Department of Cardiology, St Antonius Hospital, Nieuwegein, The Netherlands

Thromb Haemost 2019;119:1590–1605.

Abstract

Keywords

- patent foramen ovale
- left atrial appendage
- MitraClip
- left ventricular assist device
- device-related thrombosis

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 patent foramen ovale and left atrial appendage occluders, MitraClips/transcatheter mitral valve replacement, pacemaker leads, and left ventricular assist devices. Of note, the topic of antithrombotic therapy and thrombogenicity of prostheses in aortic position (transcatheter aortic valve replacement, surgical, mechanical, and bioprostheses) is not part of the present article and is discussed in detail in other contemporary focused articles.

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

Michal Droppa's ORCID is <https://orcid.org/0000-0001-5807-7615>.

received
 April 12, 2019
 accepted after revision
 June 21, 2019

© 2019 Georg Thieme Verlag KG
 Stuttgart · New York

DOI <https://doi.org/10.1055/s-0039-1694751>.
 ISSN 0340-6245.

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 (HF), leading to disturbances in endothelial function and impaired blood flow and composition. Protein adsorption is caused by

negatively charged hydrophilic surfaces that act 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 and MAC-1 with glycoprotein 1b α . Leucocyte degranulation contributes to a prothrombotic and proinflammatory milieu by generating free radicals, releasing interleukins and tumor necrosis factor α , and activating monocytes, leading to induction of tissue factor expression and consequent initiation of the coagulation cascade (→ Fig. 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

Fig. 1 Mechanism of contact activation on artificial surface leading to device thrombosis (figure was composed by using Adobe Stock vectors). DTI, direct thrombin inhibitor; IL, interleukin; MAC-1, macrophage-1 antigen; PSGL1, P-Selectin glycoprotein ligand-1; TF, tissue factors; TNF, tumor necrosis factor; VKA, vitamin k antagonists; vWF, von Willebrand factor.

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/American Stroke Association.

In addition, we searched for relevant ongoing clinical trials in the registry of clinical trials (clinicaltrials.gov) using keywords “Mitral interventions,” “left atrial appendage (LAA) occlusion,” “antithrombotic treatment,” and “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,” “LAA,” “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 Closure Device Thrombosis

Indications for patent foramen ovale (PFO) occluders have recently increased in patients with cryptogenic stroke/embolic stroke of undetermined source 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 with antiplatelet therapy.⁴ To date, there is lack of data regarding the benefits of PFO occluder compared with 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 was usually lower compared with 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 used⁷ and systematic transesophageal echocardiography (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 the type of occluder and duration of follow-up (→ Fig. 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 Although 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 → Fig. 3C and ref. ¹⁵). It is a 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

Fig. 2 Reported locations and frequencies of device-related thrombosis after implantation of endocardiac devices.

Fig. 3 (A) Two-dimensional (2D) transesophageal echocardiography (TOE) images and (B) three-dimensional (3D) TOE images of device-related thrombosis (DRT) 6 weeks after left atrial appendage (LAA) occluder (Amplatzer Cardiac Plug) in a 70-year-old patient. (C) DRT 3.5 months after patent foramen ovale (PFO) occluder implantation in a 68-year-old patient. (D) Pacemaker-associated thrombosis on atrial lead in a patient with sick-sinus-syndrome.

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 1 to 6 months DAPT 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 meta-analysis, 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, postimplantation 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 fac-

tors), 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 vs. > 45 days after implantation) has been proposed by Elgendy et al.¹⁶

Anticoagulation using vitamin K antagonists (VKAs) with tight international normalized ratio (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 glycoprotein (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 Closure Device Thrombosis

Several LAA occluder (LAAO) devices have been developed including the WATCHMAN (Boston Scientific), the AMPLATZER Cardiac Plug, and the second-generation AMPLATZER Amulet

LAAO (Abbott). The Lariat system is an extracardiac interventional device and therefore not part of this focused article on endocardial devices. Most experience from randomized and/or postmarketing 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 computed tomography 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, postprocedural antithrombotic regimen, and clinical risk factors. In a systematic echocardiographic evaluation, thrombi were predominantly observed within

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 postimplant)
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 available in 63% of patients)	Aspirin monotherapy in one-third of patients	No impact on stroke rates

Abbreviations: APT, antiplatelet therapy; ASA, acetylsalicylic acid; CT, computed tomography; DAPT, dual antiplatelet therapy; DRT, device-related thrombosis; FU, follow-up; ICB, intracranial bleeding; LAA, left atrial appendage; LAAO, left atrial appendage occluder; OAC, oral anticoagulant; TIA, transient ischemic attack; TOE, transesophageal echocardiography; SAPT, single-antiplatelet therapy.

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, ► **Fig. 3A, B**) or on the polyethylene terephthalate 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 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 with patients without DRT.²⁴ AFIB burden has also been discussed as a potential risk for LAAO DRT.²¹ Clopidogrel nonresponsiveness measured by platelet function testing has been associated with DRT in one study²⁷ and showed an association with bleeding events and not with DRT after LAAO implantation in another cohort study.²⁸

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 with VKA alone in patients without LAAO. According to current expert opinions, DAPT 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 (► **Fig. 4**). The efficacy and safety of occluding the LAA compared with medical therapy is a matter of investigation in several ongoing trials. Several trials are currently testing the superiority of endocardial LAAO followed by antiplatelet therapy compared with best medical care, including nonvitamin K-antagonists (NOACs) therapy in patients with AFIB (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 postprocedural phase might be reasonable, that is, treating patients with risk factors for DRT such as reduced left ventricular ejection fraction, larger LA, high CHA₂DS₂-VASc score, or incomplete sealing of the device with a short course of an oral anticoagulant (OAC) 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 bailout 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) trial³⁸ in different functional MR/HF populations. HF 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 HF. 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%), and 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

Fig. 4 Predominant oral antithrombotic protocols (shown as percentage) in the long-term phase (> 6 months) postendocardial left atrial appendage occluder (LAAO) implantation in patients without contraindications to vitamin K antagonist (VKA) or nonvitamin K-antagonist (NOAC) and no leak during follow-up transesophageal echocardiography (TOE) (A), in patients with absolute contraindications to VKA or NOAC and LAA leak > 5 mm (B), or device thrombus (C) during follow-up transesophageal echocardiography (multiple answers allowed); according to the European Heart Rhythm Association (EHRA) survey among 33 European centers, modified according to Tilz et al.³⁴

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 Several 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 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 (→ Fig. 5). 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 a treatment option in high-risk surgical patients by using transcatheter aortic valve replacement (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 a 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 (UFH) 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

Fig. 5 Case of left atrial appendage (LAA) thrombosis shortly after MitraClip implantation due to altered hemodynamics and increased thrombogenicity measured by thrombelastography. (A) Pre-interventional TOE revealing functional mitral regurgitation (MR) grade III. (B) Absence of left atrial thrombi pre-intervention. (C) To evaluate the influence of reducing MR on thrombogenicity TBG was performed before PMVR. (D) TOE image documenting successful reduction of MR to grade I. (E) TOE right after deployment of the clip reveals a highly increased spontaneous echo contrast and the acute formation of a solid thrombus in the left atrial appendix. (F) Thrombelastography done after PMVR documents a decreased time to thrombus initiation (R) as well as an increased thrombus building time (α) and maximum amplitude (MA) in comparison to the pre-interventional measurements. The measured activated clotting time was above 380 s (figure reproduced with permission from Glatthaar et al⁴⁴).

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 DAPT in patients undergoing the MitraClip procedure

who have no AFIB. In a recent monocenter 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 myocardial infarction compared with single antiplatelet therapy (72%) or DAPT (28%) only (1.4% vs. 7.6%; $p = 0.02$). There was a nonsignificant trend toward 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 OAC and one antiplatelet agent

has been frequently applied in AFIB patients⁵³ 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 bioprosthesis to TMVR.^{3,55} There is lack of evidence whether even prolonged anticoagulation or combination with antiplatelet therapy is beneficial in this setting. It is our opinion that, in patients undergoing TMVR, OAC combined with single antiplatelet should be considered due to the higher risk of prosthetic heart 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 Lead Thrombosis

Following the adoption of high-resolution echocardiography and intracardiac echocardiography (ICE), thrombotic coverage of pacemaker and implantable cardioverter-defibrillator (ICD) leads has been increasingly recognized (►Fig. 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 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 (►Fig. 3D). The presence of thrombi was significantly associated with higher pulmonary artery systolic pressure⁵⁷ and pulmonary embolism in single cases.^{58,59} 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.⁶⁰ 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.⁶¹

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 or AFIB, and thus the antithrombotic regimen is very heterogeneous.⁶² In patients already pretreated with NOACs, pacemaker insertion can be performed without stopping the anticoagulant to reduce the thrombotic risk in the early postprocedural phase.⁶³ 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 (tPA).^{60,64–66}

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.⁶⁰

Risk Factors for Thrombosis of Cardiac Assist Devices

Extracorporeal Life Support, Impella

Extracorporeal life support (ECLS) using extracorporeal membrane oxygenation (ECMO) is associated with disturbances in coagulation. Use of both venovenous and venoarterial 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 to consumption of coagulation factors, in particular factor VIII, consumption of platelets by activation, and shear-induced modulation of vWF multimers. On the other hand, ECMO provides a large artificial surface, which stimulates procoagulatory and proinflammatory processes. Different components have been identified to influence platelet-activating and procoagulatory 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 Impella ventricular assist device (2.5, CP, 5.0, RP, Abiomed) have been described in only a 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 preexisting ventricular thrombus.

Left Ventricular Assist Devices

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.^{72–75} LVAD thrombosis is a life-threatening 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.^{72–75}

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.⁷² Improved implant techniques and consistent postoperative 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 with 15.7% of the patients who received the axial flow pump group (hazard ratio, 0.06; 95% CI, 0.01–0.26; $p < 0.001$).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 (preexisting ventricular and/or atrial

thrombus, noncompliance 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 (► Fig. 6).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 nonsurgical options, including thrombolytic and antithrombotic therapies (i.e., direct thrombin inhibitor, tPA, or GPIIb/IIIa antagonist).^{79–82}

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.^{83,84} 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

Fig. 6 Proposed algorithm for diagnosis and management of left ventricular assist device (LVAD) thrombosis (Figure reproduced with permission from Goldstein et al⁷⁸).

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 are still numerous patients on the second 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 indication for antiplatelet or anticoagulant treatment (e.g., within 6 months of DAPT after percutaneous coronary intervention or in AFIB patients with high stroke risk receiving OAC). Pacemaker implantation should be performed under continued antithrombotic therapy unless the patient is at very high perioperative bleeding risk according to results of recent randomized controlled trials and guideline recommendations.^{63,89,90} There are currently no systematic protocols regarding periprocedural 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 risks. 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 anticoagulant effect is desirable. For instance, a patient undergoing MitraClip with a 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 instructions for use and guideline recommendations, intraprocedural activated clotting time (ACT) using UFH should be 250 to 300 seconds for LAAO, at least 200 seconds for PFO/atrial septal defect (ASD) closure, and 250 to 300 seconds for MitraClip.⁹¹ OAC should be reinitiated as soon as feasible, depending on the postinterventional bleeding risk. Temporary low-dose heparinization might be applicable to prevent periprocedural thrombotic events while avoiding access site bleeding risk. Loading with clopidogrel (300–600 mg) should take place prior to procedure for LAAO, the day before PFO occlusion and directly after MitraClip according to protocols, clinical trials, and IFUs^{7,92,93} (→Fig. 7). Systematic trials investigating the extent and the timing of periprocedural antiplatelet therapy are lacking.

Management of Periprocedural Antithrombotic Therapy in Cardiac Assist Device Therapy

Extracorporeal 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 ECLS, heparinization aiming for an ACT of 180 to 220 seconds is mandatory; however, clinical scenarios in these critically ill patients sometimes require modifications of these target values.

There is currently no consensus on how to control exaggerated platelet consumption under ECLS. After careful exclusion of heparin-induced thrombocytopenia, pharmacological platelet inhibition with short-acting compounds (e.g., intravenous P2Y₁₂ inhibitor cangrelor) have been used in some case reports showing favorable outcome,⁹⁴ while bleeding was still frequent.⁹⁵ In an animal model and in vitro model of extracorporeal 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 hemostatic monitoring should be integrated to early detect and counteract thrombotic alterations.

There are no standardized anticoagulation protocols in patients treated with Impella. Heparinization with an ACT of 160 to 180 seconds is recommended by the manufacturer. 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 was associated with low thrombotic events rates.⁹⁸

Left Ventricular Assist Devices

During LVAD surgery with cardiopulmonary bypass, 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 to 400 U/kg plus additional doses to achieve and maintain an ACT of greater than 450 seconds if necessary, use of a heparin dose–response technique can 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 seconds; it is progressively increased to 55 to 60 seconds within the first 48 to 72 hours after surgery. Accompanying UFH administration, oral anticoagulation with a VKA should be started once the clinical condition is stable and oral intake is feasible. The INR target should be between 2.0 and 3.5 according to device company recommendations for modern LVADs. However, there is

Antithrombotic therapies after implantation of endocardial devices/LVAD				
MitraClip	PFO-closure	LAA-closure	Pacemaker-/ ICD - implantation	LVAD
Periprocedural antithrombotic therapy				
<ul style="list-style-type: none"> Heparinization, ACT 250-300 Clopidogrel 300-600mg right after the procedure 	<ul style="list-style-type: none"> Heparinization, ACT ≥ 200 s Clopidogrel 300-600mg the day before procedure 	<ul style="list-style-type: none"> Heparinization, ACT 250-300 Clopidogrel 300-600mg before the procedure 	<ul style="list-style-type: none"> No specific therapy 	<ul style="list-style-type: none"> ACT ~ 450 sec during CPB, pTT post-op increased to 55-60 s within 48-72 h
Postprocedural antithrombotic therapy				
Sinus rhythm: <ul style="list-style-type: none"> DAPT (ASA+clopidogrel) for 3 months Consider shortterm (4-week) OAC +/- APT in particular in patients with enhanced thrombogenicity e.g. low flow in LA, history of stroke and tolerable bleeding risk followed by APT AFIB: <ul style="list-style-type: none"> (N)OAC monotherapy 	<ul style="list-style-type: none"> DAPT (ASA + clopidogrel) for 3 to 6 months, followed by antiplatelet monotherapy (ASA) TOE at the time of cessation of DAPT 	<ul style="list-style-type: none"> DAPT (ASA + clopidogrel) for 3 months, followed by ASA monotherapy In patients with increased bleeding risk, e.g. high intracranial bleeding risk consider antiplatelet monotherapy (ASA) In patients with high thromboembolic risk and/or suboptimal device placement and tolerable bleeding risk consider shortterm OAC 	<ul style="list-style-type: none"> No specific antithrombotic therapy, antithrombotic therapy defined by underlying disease (e.g. antiplatelet therapy in case of ischemic heart disease, OAC preferably NOAC in case of AFIB) 	<ul style="list-style-type: none"> Unfractionated heparin ASA (life long) Bridging unfractionated heparin to oral vitamin k antagonist (life long)
Strategy in case of device related thrombosis				
<ul style="list-style-type: none"> Shortterm OAC (VKA) guided by TOE Screening for AFIB, if positive, switching to permanent OAC (preferably NOAC) 	<ul style="list-style-type: none"> In case of DRT with small thrombi in TOE consider OAC (VKA) With large thrombi surgical removal + subsequent surgical closure; In case of high surgical risk and tolerable bleeding risk, thrombolytic therapy +/- GPI 	<ul style="list-style-type: none"> If smaller thrombi, OAC (VKA) for 4 weeks, control by TOE With large thrombi surgical removal + subsequent surgical closure; In case of high surgical risk and tolerable bleeding risk, thrombolytic therapy +/- GPI 	<ul style="list-style-type: none"> If large thrombi, bleeding risk is low and increased pulmonary pressure, consider short-term Heparinization/OAC or thrombolytic therapy Interventional /surgical retrieval in high bleeding risk patients and/or unclear diagnosis 	<ul style="list-style-type: none"> Medical intervention: Systemic or local lysis Surgical intervention: Pump exchange

Fig. 7 Proposed algorithm for antithrombotic therapy based on risk stratification following cardiac device therapy.

inconsistency in the literature as to whether antiplatelet therapy is required and what dose of therapy should be administered. Recently, a systematic review has shown that most centers start 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 as to 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 risks. This will enable careful selection of patients who benefit from cardiac prostheses or who might be better treated with best medical

care or nonprosthetic implant methods like the NobleStitch for PFO or the Lariat for LAA occlusion. Current biomaterial research focuses on synthesizing less thrombogenic biomaterials. Innovative techniques in tissue engineering, application of stem cell technology, and coating with biologically active, antithrombotic compounds (e.g., polyethylene glycol-corn trypsin inhibitor coated surfaces) in valve and device development might help to improve bioavailability and help to avoid the need for systemic antithrombotic therapy. Finally, novel strategies of antithrombotic treatment, like factor XI/XIa or XII/XIIa inhibition using small-molecule inhibitors, antibodies, or antisense oligonucleotides, are currently in the pipeline and represent attractive strategies to inhibit the contact activation pathway on artificial devices.^{1,102,103}

Conclusion

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

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.

What does this paper add?

- This article 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.

Funding

This project was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) Klinische Forschungsgruppe-KFO-274 "Platelets - Molecular Mechanisms and Translational Implications" (Project number 190538538) and TRR 240 "Platelets - Molecular, cellular and systemic functions in health and disease" (Project number 374031971).

Conflict of Interest

A.-F.P. reports personal fees from HeartWare Inc, outside the submitted work. A.R. reports personal fees from AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, and BMS/Pfizer, outside the submitted work. D.A. reports personal fees from Roche Diagnostics, DSI/Lilly, AstraZeneca, Pfizer, Bayer AG, and MSD Pharma, outside the submitted work. D.G. reports grants from Roche Diagnostics, DSI/Lilly, AstraZeneca, Pfizer, Bayer AG, and MSD Pharma, outside the submitted work. D.S. reports grants and personal fees from Roche Diagnostics and

Daiichi Sankyo, personal fees from Bayer, AstraZeneca, Pfizer, and Sanofi, outside the submitted work. J.T.B. reports grants and personal fees from AstraZeneca, personal fees from Eli Lilly, Daiichi Sankyo, The Medicines Company, Accu-Metrics, Boehringer Ingelheim, BMS, Pfizer, Bayer, Ferrer, and ZonMw, outside the submitted work. K.H. reports personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Portola, and Sanofi Aventis, outside the submitted work. R.F.S. reports grants, personal fees and other from AstraZeneca, Bayer, Bristol-Myers Squibb/Pfizer alliance, and PlaqueTec, personal fees from Avacta, Haemonetics, Novartis, and Thromboserin, outside the submitted work. S.D.K. reports personal fees from Aspen, AstraZeneca, Bayer, and BMS/Pfizer, outside the submitted work. T.G. reports personal fees from AstraZeneca, Boehringer Ingelheim, Pfizer, Boston Scientific, Abbott, grants and personal fees from Bayer Healthcare, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Medtronic, personal fees from Ferrer, outside the submitted work.

Acknowledgments

The authors thank Thomas Müller, FRG, CRONA, University Hospital Tübingen, for his excellent technical support in figure designing.

References

- 1 Jaffer IH, Fredenburgh JC, Hirsh J, Weitz JI. Medical device-induced thrombosis: what causes it and how can we prevent it? *J Thromb Haemost* 2015;13(Suppl 1):S72–S81
- 2 Wright SD, Weitz JI, Huang AJ, Levin SM, Silverstein SC, Loike JD. Complement receptor type three (CD11b/CD18) of human polymorphonuclear leukocytes recognizes fibrinogen. *Proc Natl Acad Sci U S A* 1988;85(20):7734–7738
- 3 Baumgartner H, Falk V, Bax JJ, et al; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38(36):2739–2791
- 4 Pristipino C, Sievert H, D'Ascenzo F, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *Eur Heart J* [Internet]; 2018. Available at: <https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehy649/5144593>. Accessed January 2, 2019
- 5 Saver JL, Carroll JD, Thaler DE, et al; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;377(11):1022–1032
- 6 Søndergaard L, Kasner SE, Rhodes JF, et al; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017;377(11):1033–1042
- 7 Mas J-L, Derumeaux G, Guillon B, et al; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017;377(11):1011–1021
- 8 Kuijpers T, Spencer FA, Siemieniuk RAC, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke? A clinical practice guideline. *BMJ* 2018;362:k2515
- 9 Snijder RJR, Renes LE, Suttorp MJ, Ten Berg JM, Post MC. Percutaneous patent foramen ovale closure using the Occlutech Figulla device: more than 1,300 patient-years of follow up. *Catheter Cardiovasc Interv* 2019;93(06):1080–1084

- 10 Rudolph V, Augustin J, Hofmann T, et al. Predictors of recurrent stroke after percutaneous closure of patent foramen ovale. *EuroIntervention* 2014;9(12):1418–1422
- 11 Mariucci E, Donti A, Salomone L, et al. Recurrent stroke after transcatheter PFO closure in cryptogenic stroke or TIA: long-term follow-up. *Cardiol Res Pract* 2017;2017:9849425
- 12 Wöhrle J, Bertrand B, Söndergaard L, et al. PFO closure and Cryptogenic Stroke (PRECISE) registry: a multi-center, international registry. *Clin Res Cardiol* 2012;101(10):787–793
- 13 Abaci A, Unlu S, Alsancak Y, Kaya U, Sezenoz B. Short and long term complications of device closure of atrial septal defect and patent foramen ovale: meta-analysis of 28,142 patients from 203 studies. *Catheter Cardiovasc Interv* 2013;82(07):1123–1138
- 14 Wahl A, Tai T, Praz F, et al. Late results after percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism using the Amplatzer PFO occluder without intra-procedural echocardiography: effect of device size. *JACC Cardiovasc Interv* 2009;2(02):116–123
- 15 Klotz S, Gebhard M, Sievers HH. Late left atrial thrombosis of an Amplatzer patent foramen ovale occluder. *J Thorac Cardiovasc Surg* 2011;142(05):1270–1271
- 16 Elgendy AY, Elgendy IY, Mojaidi MK, et al. New-onset atrial fibrillation following percutaneous patent foramen ovale closure: a systematic review and meta-analysis of randomised trials. *EuroIntervention* 2019;14(17):1788–1790
- 17 Luc JGY, Bakar SN, Kiai B, Sridhar K. Thrombus in a hypercoagulable patient following patent foramen ovale closure with the gore septal occluder. *JACC Cardiovasc Interv* 2018;11(11):1108–1109
- 18 Vanderheyden M, Willaert W, Claessens P, Branders I, Ex P, Vermeersch P. Thrombosis of a patent foramen ovale closure device: thrombolytic management. *Catheter Cardiovasc Interv* 2002;56(04):522–526
- 19 Lempereur M, Aminian A, Freixa X, et al. Device-associated thrombus formation after left atrial appendage occlusion: a systematic review of events reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet. *Catheter Cardiovasc Interv* 2017;90(05):E111–E121
- 20 Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation* 2011;123(04):417–424
- 21 Dukkipati SR, Kar S, Holmes DR, et al. Device-related thrombus after left atrial appendage closure. *Circulation* 2018;138(09):874–885
- 22 Cochet H, Iriart X, Sridi S, et al. Left atrial appendage patency and device-related thrombus after percutaneous left atrial appendage occlusion: a computed tomography study. *Eur Heart J Cardiovasc Imaging* 2018;19(12):1351–1361
- 23 Pracon R, Bangalore S, Zielinska Z, et al. Device thrombosis after percutaneous left atrial appendage occlusion is related to patient and procedural characteristics but not to duration of postimplantation dual antiplatelet therapy. *Circ Cardiovasc Interv* 2018;11(03):e005997 Page: 1
- 24 Sedaghat A, Schrickel J-W, Andrié R, Schueler R, Nickenig G, Hammerstingl C. Thrombus formation after left atrial appendage occlusion with the Amplatzer Amulet device. *JACC Clin Electrophysiol* 2017;3(01):71–75
- 25 Kubo S, Mizutani Y, Meemook K, Nakajima Y, Hussaini A, Kar S. Incidence, characteristics, and clinical course of device-related thrombus after Watchman left atrial appendage occlusion device implantation in atrial fibrillation patients. *JACC Clin Electrophysiol* 2017;3(12):1380–1386
- 26 Fauchier L, Cinaud A, Brigadeau F, et al. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. *J Am Coll Cardiol* 2018;71(14):1528–1536
- 27 Ketterer U, D'Ancona G, Siegel I, Ortak J, Ince H, Kische S. Percutaneous left atrial appendage occlusion: device thrombosis in clopidogrel non-responders. *Int J Cardiol* 2016;204:196–197
- 28 Dannenberg L, Mourikis P, Naguib D, et al. Antiplatelet effects of aspirin and clopidogrel after left atrial appendage (LAA) occluder implantation. *Int J Cardiol* 2019;275:95–100
- 29 Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013;61(25):2551–2556
- 30 Saw J, Tzikas A, Shakir S, et al. Incidence and clinical impact of device-associated thrombus and peri-device leak following left atrial appendage closure with the Amplatzer Cardiac Plug. *JACC Cardiovasc Interv* 2017;10(04):391–399
- 31 Tzikas A, Freixa X, Lull L, et al. Patients with intracranial bleeding and atrial fibrillation treated with left atrial appendage occlusion: results from the Amplatzer Cardiac Plug registry. *Int J Cardiol* 2017;236:232–236
- 32 Tzikas A, Shakir S, Gafoor S, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *EuroIntervention* 2016;11(10):1170–1179
- 33 Pison L, Potpara TS, Chen J, Larsen TB, Bongiorno MG, Blomström-Lundqvist C; Scientific Initiative Committee, European Heart Rhythm Association. Left atrial appendage closure-indications, techniques, and outcomes: results of the European Heart Rhythm Association Survey. *Europace* 2015;17(04):642–646
- 34 Tilz RR, Potpara T, Chen J, et al. Left atrial appendage occluder implantation in Europe: indications and anticoagulation post-implantation. Results of the European Heart Rhythm Association Survey. *Europace* 2017;19(10):1737–1742
- 35 Lam SCC, Bertog S, Sievert H. Incomplete left atrial appendage occlusion and thrombus formation after Watchman implantation treated with anticoagulation followed by further transcatheter closure with a second-generation Amplatzer Cardiac Plug (Amulet device). *Catheter Cardiovasc Interv* 2015;85(02):321–327
- 36 Stimpfle F, Müller K, Geisler T, et al. Thromboembolic risk reduction via transseptal thrombus aspiration in a patient with spontaneous left atrial thrombus and stroke. *JACC Cardiovasc Interv* 2017;10(06):e57–e59
- 37 Obadia J-F, Messika-Zeitoun D, Leurent G, et al; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;379(24):2297–2306
- 38 Stone GW, Lindenfeld J, Abraham WT, et al; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;379(24):2307–2318
- 39 Adelborg K, Szépligeti S, Sundbøll J, et al. Risk of stroke in patients with heart failure: a population-based 30-year cohort study. *Stroke* 2017;48(05):1161–1168
- 40 Puls M, Lubos E, Boekstegers P, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. *Eur Heart J* 2016;37(08):703–712
- 41 Huntgeburth M, Müller-Ehmsen J, Brase C, Baldus S, Rudolph V. Thrombus formation at the MitraClip system during percutaneous mitral valve repair. *JACC Cardiovasc Interv* 2014;7(09):e111–e112
- 42 Hamm K, Barth S, Diegeler A, Kerber S. Stroke and thrombus formation appending to the MitraClip: what is the appropriate anticoagulation regimen? *J Heart Valve Dis* 2013;22(05):713–715
- 43 Bekeredjian R, Mereles D, Pleger S, Krumdorf U, Katus HA, Rottbauer W. Large atrial thrombus formation after MitraClip implantation: is anticoagulation mandatory? *J Heart Valve Dis* 2011;20(02):146–148
- 44 Glatthaar A, Seizer P, Patzelt J, Langer H, Schrieck J, Gawaz M. Formation of a left atrial thrombus during percutaneous mitral

- valve edge-to-edge repair induced by acute reduction of mitral regurgitation. *J Cardiol Cases* 2017;17(01):33–35
- 45 Orban M, Braun D, Sonne C, et al. Dangerous liaison: successful percutaneous edge-to-edge mitral valve repair in patients with end-stage systolic heart failure can cause left ventricular thrombus formation. *EuroIntervention* 2014;10(02):253–259
 - 46 Maleki K, Mohammadi R, Hart D, Cotiga D, Farhat N, Steinberg JS. Intracardiac ultrasound detection of thrombus on transseptal sheath: incidence, treatment, and prevention. *J Cardiovasc Electrophysiol* 2005;16(06):561–565
 - 47 Eng MH, Greenbaum A, Wang DD, et al. Thrombotic valvular dysfunction with transcatheter mitral interventions for post-surgical failures. *Catheter Cardiovasc Interv* 2017;90(02):321–328
 - 48 Dangas GD, Weitz JI, Giustino G, Makkar R, Mehran R. Prosthetic heart valve thrombosis. *J Am Coll Cardiol* 2016;68(24):2670–2689
 - 49 Regueiro A, Granada JF, Dagenais F, Rodés-Cabau J. Transcatheter mitral valve replacement: insights from early clinical experience and future challenges. *J Am Coll Cardiol* 2017;69(17):2175–2192
 - 50 Muller DWM, Farivar RS, Jansz P, et al; Tendyne Global Feasibility Trial Investigators. Transcatheter mitral valve replacement for patients with symptomatic mitral regurgitation: a global feasibility trial. *J Am Coll Cardiol* 2017;69(04):381–391
 - 51 Frerker C, Schlüter M, Sanchez OD, et al. Cerebral protection during MitraClip implantation: initial experience at 2 centers. *JACC Cardiovasc Interv* 2016;9(02):171–179
 - 52 Seeger J, Markovic S, Kessler M, Rottbauer W, Wöhrle J. Apixaban after percutaneous edge-to-edge mitral valve repair in patients with maintained sinus rhythm. *JACC Cardiovasc Interv* 2019;12(02):214–216
 - 53 Eggebrecht H, Schelle S, Puls M, et al. Risk and outcomes of complications during and after MitraClip implantation: experience in 828 patients from the German TRAns catheter mitral valve interventions (TRAMI) registry. *Catheter Cardiovasc Interv* 2015;86(04):728–735
 - 54 Geis N, Raake P, Kiriakou C, et al. Temporary oral anticoagulation after MitraClip – a strategy to lower the incidence of post-procedural stroke? *Acta Cardiol* 2019;1–7
 - 55 Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;70(02):252–289
 - 56 Rahbar AS, Azadani PN, Thatipelli S, Fleischmann KE, Nguyen N, Lee BK. Risk factors and prognosis for clot formation on cardiac device leads. *Pacing Clin Electrophysiol* 2013;36(10):1294–1300
 - 57 Supple GE, Ren J-F, Zado ES, Marchlinski FE. Mobile thrombus on device leads in patients undergoing ablation: identification, incidence, location, and association with increased pulmonary artery systolic pressure. *Circulation* 2011;124(07):772–778
 - 58 D'Aloia A, Bonadei I, Vizzardi E, Curnis A. Right giant atrial thrombosis and pulmonary embolism complicating pacemaker leads. *BMJ Case Rep* 2013;2013:bcr2012008017–bcr2012008017
 - 59 Karavidas A, Lazaros G, Matsakas E, et al. Early pacemaker lead thrombosis leading to massive pulmonary embolism. *Echocardiography* 2004;21(05):429–432
 - 60 Salaun E, Deharo J-C, Casalta JP, et al. An oscillating mass attached to a pacemaker lead: thrombus or vegetation? A fishing story. *JACC Clin Electrophysiol* 2017;3(08):915–916
 - 61 Korkeila P, Mustonen P, Koistinen J, et al. Clinical and laboratory risk factors of thrombotic complications after pacemaker implantation: a prospective study. *Europace* 2010;12(06):817–824
 - 62 Ghanbari H, Nallamothu BK, Wang Y, Curtis JP. Antithrombotic therapy and outcomes after ICD implantation in patients with atrial fibrillation and coronary artery disease: an analysis from the National Cardiovascular Data Registry (NCDR)®. *J Am Heart Assoc* 2015;4(02):pii: e001331
 - 63 Steffel J, Verhamme P, Potpara TS, et al; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39(16):1330–1393
 - 64 May KJ Jr, Cardone JT, Stroebel PP, Riba AL. Streptokinase dissolution of a right atrial thrombus associated with a temporary pacemaker. *Arch Intern Med* 1988;148(04):903–904
 - 65 Goldhaber SZ, Nagel JS, Théard M, Levine JD, Sutton MG. Treatment of right atrial thrombus with urokinase. *Am Heart J* 1988;115(04):894–897
 - 66 Cooper CJ, Dweik R, Gabbay S. Treatment of pacemaker-associated right atrial thrombus with 2-hour rTPA infusion. *Am Heart J* 1993;126(01):228–229
 - 67 Mandal S, Pande A, Mandal D, et al. Permanent pacemaker-related upper extremity deep vein thrombosis: a series of 20 cases. *Pacing Clin Electrophysiol* 2012;35(10):1194–1198
 - 68 Fuchs G, Berg N, Broman LM, Pahl Wittberg L. Flow-induced platelet activation in components of the extracorporeal membrane oxygenation circuit. *Sci Rep* 2018;8(01):13985
 - 69 Kirklin JK, Naftel DC, Pagani FD, et al. Long-term mechanical circulatory support (destination therapy): on track to compete with heart transplantation? *J Thorac Cardiovasc Surg* 2012;144(03):584–603, discussion 597–598
 - 70 Rogers JG, Pagani FD, Tatooles AJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. *N Engl J Med* 2017;376(05):451–460
 - 71 Slaughter MS, Rogers JG, Milano CA, et al; HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;361(23):2241–2251
 - 72 Kirklin JK, Naftel DC, Kormos RL, et al. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device. *J Heart Lung Transplant* 2014;33(01):12–22
 - 73 Miller LW, Pagani FD, Russell SD, et al; HeartMate II Clinical Investigators. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007;357(09):885–896
 - 74 Pagani FD, Miller LW, Russell SD, et al; HeartMate II Investigators. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol* 2009;54(04):312–321
 - 75 Starling RC, Moazami N, Silvestry SC, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. *N Engl J Med* 2014;370(01):33–40
 - 76 Klodell CT, Massey HT, Adamson RM, et al. Factors related to pump thrombosis with the Heartmate II left ventricular assist device. *J Card Surg* 2015;30(10):775–780
 - 77 Mehra MR, Goldstein DJ, Uriel N, et al; MOMENTUM 3 Investigators. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. *N Engl J Med* 2018;378(15):1386–1395
 - 78 Goldstein DJ, John R, Salerno C, et al. Algorithm for the diagnosis and management of suspected pump thrombus. *J Heart Lung Transplant* 2013;32(07):667–670
 - 79 Sylvia LM, Ordway L, Pham DT, DeNofrio D, Kiernan M. Bivalirudin for treatment of LVAD thrombosis: a case series. *ASAIO J* 2014;60(06):744–747
 - 80 Badiye A, Hernandez GA, Chaparro S. Argatroban as novel therapy for suspected thrombosis in patients with continuous-flow left ventricle assist device and hemolysis. *ASAIO J* 2014;60(03):361–365
 - 81 Muthiah K, Robson D, Macdonald PS, et al. Thrombolysis for suspected intrapump thrombosis in patients with continuous flow centrifugal left ventricular assist device. *Artif Organs* 2013;37(03):313–318
 - 82 Tellor BR, Smith JR, Prasad SM, Joseph SM, Silvestry SC. The use of eptifibatide for suspected pump thrombus or thrombosis in patients with left ventricular assist devices. *J Heart Lung Transplant* 2014;33(01):94–101

- 83 Schlendorf K, Patel CB, Gehrig T, et al. Thrombolytic therapy for thrombosis of continuous flow ventricular assist devices. *J Card Fail* 2014;20(02):91–97
- 84 Garbade J, Bittner HB, Mohr F-W, Barten MJ. Fluoroscopy-guided resolution of ingested thrombus leading to functional disturbance of a continuous-flow left ventricular assist device. *Case Rep Surg* 2012;2012:791056
- 85 Köksel U, Erbasan O, Bayezid Ö, et al. Thrombosis in continuous flow left ventricular assist devices: our clinical experience with medical and surgical management. *Transplant Proc* 2016;48(06):2162–2167
- 86 Bartoli CR, Ailawadi G, Kern JA. Diagnosis, nonsurgical management, and prevention of LVAD thrombosis. *J Card Surg* 2014;29(01):83–94
- 87 Radwan M, Risteski P, Hoffmann R, Popov AF. Repeat left ventricular assist device exchange with inflow or outflow correction for recurrent pump thrombosis and cerebral haemorrhage through limited incisions. *Eur J Cardiothorac Surg* 2018;54(04):781–783
- 88 Hanke JS, Rojas SV, Dogan G, et al. First series of left ventricular assist device exchanges to HeartMate 3. *Eur J Cardiothorac Surg* 2017;51(05):887–892
- 89 Birnie DH, Healey JS, Wells GA, et al; BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013;368(22):2084–2093
- 90 Birnie DH, Healey JS, Wells GA, et al. Continued vs. interrupted direct oral anticoagulants at the time of device surgery, in patients with moderate to high risk of arterial thromboembolic events (BRUISE CONTROL-2). *Eur Heart J* 2018;39(44):3973–3979
- 91 Widimský P, Kočka V, Roháč F, Osmančík P. Periprocedural antithrombotic therapy during various types of percutaneous cardiovascular interventions. *Eur Heart J Cardiovasc Pharmacother* 2016;2(02):131–140
- 92 Meier B, Blaauw Y, Khattab AA, et al; Document Reviewers. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *Europace* 2014;16(10):1397–1416
- 93 Feldman T, Wasserman HS, Herrmann HC, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. *J Am Coll Cardiol* 2005;46(11):2134–2140
- 94 Droppa M, Vaduganathan M, Venkateswaran RV, et al. Cangrelor in cardiogenic shock and after cardiopulmonary resuscitation: A global, multicenter, matched pair analysis with oral P2Y₁₂ inhibition from the IABP-SHOCK II trial. *Resuscitation* 2019;137:205–212
- 95 Ciolek AM, Ma K, Jennings DL, et al. Use of cangrelor during venoarterial extracorporeal membrane oxygenation following percutaneous coronary intervention. *J Heart Lung Transplant* 2019;38:S307
- 96 Krajewski S, Kurz J, Neumann B, et al. Short-acting P2Y₁₂ blockade to reduce platelet dysfunction and coagulopathy during experimental extracorporeal circulation and hypothermia. *Br J Anaesth* 2012;108(06):912–921
- 97 Alhussein M, Moayed Y, Posada JD, et al. Ventricular Thrombosis Post-Venoarterial Extracorporeal Membrane Oxygenation. *Circ Heart Fail* 2017;10(02):pii: e003757
- 98 Batra S, Kamran H, Lech T, et al. High thromboembolic event rate in patients supported with an Impella CP device with an anti-Xa level of less than 0.1 u/mL. *J Heart Lung Transplant* 2018;37:S59
- 99 Potapov EV, Antonides C, Crespo-Leiro MG, et al. 2019 EACTS Expert Consensus on long-term mechanical circulatory support. *Eur J Cardiothorac Surg* 2019;2019:ezz098
- 100 Ichikawa J, Mori T, Kodaka M, Nishiyama K, Ozaki M, Komori M. Changes in heparin dose response slope during cardiac surgery: possible result in inaccuracy in predicting heparin bolus dose requirement to achieve target ACT. *Perfusion* 2017;32(06):474–480
- 101 Baumann Kreuziger LM, Kim B, Wieselthaler GM. Antithrombotic therapy for left ventricular assist devices in adults: a systematic review. *J Thromb Haemost* 2015;13(06):946–955
- 102 Larsson M, Rayzman V, Nolte MW, et al. A factor XIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk. *Sci Transl Med* 2014;6:222ra17–222ra17
- 103 Weitz JI, Fredenburgh JC. Factors XI and XII as targets for new anticoagulants. *Front Med (Lausanne)* 2017;4:19