Anticoagulation in cardiomyopathy: unravelling the hidden threat and challenging the threat individually

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Abstract

Cardiomyopathy comprises a heterogeneous group of myocardial abnormalities, structural or functional in nature, in the absence of coronary artery disease and other abnormal loading conditions. These myocardial pathologies can result in premature death or disability from progressive heart failure, arrhythmia, stroke, or other embolic events. The European Cardiomyopathy Registry reports a high stroke risk in cardiomyopathy patients ranging from 2.1% to 4.5%, as well as high prevalence of atrial fibrillation ranging from 14.0% to 48.5%. There is a growing interest in evaluating the risk of thromboembolism depending on the type of cardiomyopathy, as well as if anticoagulation is indicated in patients with cardiomyopathy without atrial fibrillation. Data available do not unequivocally support anticoagulation therapy in all of these patients; the management of these patients remains challenging. Many published reports pertaining to the risk of thromboembolism and consecutive treatment strategies mainly focus on single cardiomyopathy subtype. We summarize essential pathophysiological knowledge and review current literature associated with thromboembolism in various cardiomyopathy subtypes, providing recommendations for the diagnostic evaluation as well as clinical management strategies in this field. Certain cardiomyopathy subtypes require anticoagulation independent of atrial fibrillation or CHA2DS2-VASc score. Despite the scarcity of evidence regarding the choice of anticoagulation regimen (vitamin K antagonist vs. non-vitamin K oral anticoagulants) in cardiomyopathy, it is discussed and reviewed in this article. Each patient should receive a tailored strategy based on thorough clinical evaluation, published evidence, and clinical experience, due to the current recommendations mostly developed on small-sample studies or empirical evidence. The future research priorities in this area are also addressed in this article.

Keywords Cardiomyopathy; Anticoagulation; Atrial fibrillation; Embolism; Stroke

Introduction

Cardiomyopathies depict a heterogeneous group of structural or functional myocardial disturbances without coronary artery disease and other abnormal loading conditions such as valvular disease, hypertension, and congenital heart disease to explain the cardiac abnormalities. These myocardial pathologies stand for an obvious health burden because they can result in premature death or disability from progressive heart failure (HF), arrhythmia, stroke, or other embolic events. The European Cardiomyopathy Registry focusing on adult patients suffering from major subtypes of cardiomyopathy reports a high stroke risk in cardiomyopathy patients ranging from 2.1% to 4.5%, as well as high prevalence of atrial fibrillation (AF) ranging from 14.0% to 48.5%. There is a growing interest in evaluating the relationship between...
cardiomyopathy subtype, AF, and risk of thromboembolism (TE), as well as the need of anticoagulation in patients with cardiomyopathy without concomitant AF, all of which pose considerable challenges for treating physicians. However, to date, there are only limited data available regarding epidemiology and therapeutic strategies of TE in cardiomyopathy. Moreover, many published reports pertaining to the risk of TE and consecutive treatment strategies mainly focus on single cardiomyopathy subtype, and the indications for anticoagulation in AF patients with cardiomyopathy subtypes are not yet well established except for patients with hypertrophic cardiomyopathy (HCM).

This article summarizes essential epidemiologic and pathophysiological knowledge, reviewing current literature referring to TE in cardiomyopathy with emphasis on tailored anticoagulation regimens depending on the cardiomyopathy subtype, thus providing recommendations for diagnostic evaluation and clinical management strategies for the treating physician.

Pathophysiology

Despite the well-known fact that thrombus formation requires three essential prerequisites: (i) abnormal blood flow, (ii) abnormal blood constituents, and (iii) abnormalities in the vessel wall, the pathologies that could be aetiologically associated with thromboembolic diseases are not yet fully elucidated. A recent study investigating potential embolic sources in embolic stroke showed left ventricular (LV) disease, arterial disease, and atrial cardiopathy were the three most prevalent latent embolic sources, each being present in approximately 50% of all patients.10,11 Lip and Gibbs reported that the association between LV disease (cardiomyopathy, HF, and so on) and TE was based on several pathophysiological disorders like low cardiac output, dilated chambers, poor contractility, endothelial dysfunction, and others.12 For certain embolic sources like some cardiomyopathy subtypes, the low blood flow was presumed to be the main pathophysiological stimulus for thrombogenesis, predisposing to formation of red thrombi that may respond better to anticoagulation compared with aspirin for prevention of stroke recurrence.13,14 Furthermore, there is convincing evidence that cardiomyopathy predisposes to TE and its associated complications.15–19

Most patients with cardiomyopathy present with transient or progressive systolic dysfunction. This might result in intracardiac flow abnormalities in terms of blood stasis, aberrant, or turbulent flow thus predisposing to intraventricular thrombus formation.15,17,19–22 Endothelial injuries from systemic inflammation as presented in acute Takotsubo syndrome (TTS), extensive eosinophilic infiltration in hypereosinophilic syndrome (HES), or von Willebrand factor and collagen being exposed after assist device implantation facilitate not only the combination of platelets and tissue factor but also intracardiac thrombus formation and embolization. Ventricular dilatation and dysfunction, as seen in dilated cardiomyopathy (DCM) as well as catecholamine surges in TTS can induce a hypercoagulable state. An increased pro-coagulant activity can also be found in peripartum cardiomyopathy (PPCM).15,16,18,26–30 Structural and functional atrial abnormalities including increased atrial diameter, atrial standstill, and AF can increase the risk of intracardiac thrombosis, which are associated with a risk of TE and ischaemic stroke, as well as other causes of morbidity and mortality.15,31–37

These associations could help clinicians to understand the potential mechanisms of intracardiac thrombus formation and embolization in patients suffering from cardiomyopathy. This review provides a summary of the published literature regarding possible risk factors and biomarkers of TE in cardiomyopathy (Table 1).

Clinical evaluation

Clinical history and physical examination

Initial patient assessment should include demographic characteristics, family history with emphasis on cardiovascular and inflammatory disease as well as history of intracardiac thrombosis and embolic events with consecutive treatment and bleeding events, and associated extracardiac disease. Emphasis should be put on the identification of symptoms of acute or chronic HF and the presence of arrhythmias (especially AF), all of which helps to evaluate the phase of cardiomyopathy (i.e. acute, chronic, or recovery). This information might function as red flags to guide disease recognition and treatment.

Table 1 Selected risk factors and biomarkers for thromboembolism in cardiomyopathy

| Clinical risk factors | References |
|----------------------|------------|
| Female               | 30         |
| Advanced age         | 35, 38     |
| Atrial fibrillation  | 32–34      |
| Prior thromboembolism| 35         |
| Heart failure symptoms (NYHA III, IV) | 35 |
| Ventricular dilatation/dysfunction | 26 |
| Depressed left ventricular ejection fraction | 19–21 |
| Valvular regurgitation | 39, 40    |
| Increased atrial diameter | 4, 5, 31 |
| Atrial standstill    | 15, 36, 37 |
| Left ventricular apical aneurysm | 41–43 |
| Newly formed left ventricular thrombus | 44 |
| Implanted device in the ventricle | 24, 25 |
| Increase of fibrinopeptide A | 27 |
| Increase of thrombin–antithrombin III complex | 27 |
| Bromocriptine treatment (especially in PPCM) | 29 |

NYHA, New York Heart Association; PPCM, post-partum cardiomyopathy.
Physical and clinical examination allow non-invasive assessment of the patient’s current haemodynamic state and help to guide further diagnostic and therapeutic decision-making.\textsuperscript{45} Thibodeau and Drazner give an informative summary regarding the role of clinical examination in determining haemodynamic state and prognosis of the patient.\textsuperscript{45}

**Laboratory examinations**

Laboratory examinations include complete blood count, coagulation assessment, hepatic and renal function evaluation, as well as plasma levels of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-pro-BNP).

**Conventional instrument examinations**

Electrocardiogram (ECG) depicts an important tool for identifying AF and other arrhythmias. A chest X-ray should be conducted, if lung disease or HF is suspected. It can also detect enlargement of the heart cavities. A two-dimensional transthoracic echocardiogram (TTE) is essential for detecting intracardiac thrombi, assessing cardiac function as well as atrial and ventricular size in cardiomyopathy patients.

**Transesophageal echocardiography**

Compared with TTE, transesophageal echocardiography (TEE) reveals a higher sensitivity in detecting left atrial (LA) clots, a latent cause of systemic embolic events, especially in patients with AF. Recent studies confirmed that TEE could disclose an LA or left atrial appendage (LAA) clot in 5–15% of patients with AF being scheduled for cardioversion.\textsuperscript{46,47} Additionally, three-dimensional TEE examination can unveil cardiac features related to an increase risk of LA thrombus formation, including abnormalities in LAA morphology and flow velocity or spontaneous echo contrast of the LA. Therefore, TEE is highly recommended in cardiomyopathy patients with AF or cryptogenic stroke.

**Additional examinations**

Ambulatory rhythm monitoring by means of event recorders or Holter monitoring might be useful for detecting asymptomatic episodes of AF. Computed tomography (CT) scan or magnetic resonance imaging (MRI) can reveal silent strokes, thus being important for developing an individualized therapeutic anticoagulation regimen in cardiomyopathy patients.

**Epidemiology and management for thromboembolism in cardiomyopathy subtypes**

In adult patients, there are four major subtypes of cardiomyopathy: HCM, DCM, restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). Other cardiomyopathy subtypes (LV noncompaction, TTS, and so on) are also addressed in this review. Although it is well known that cardiomyopathy increases the risk of thromboembolic complications, including symptomatic or silent stroke, pulmonary embolism, and peripheral arterial embolism,\textsuperscript{2–9} only a few data are available regarding the incidence of TE in various cardiomyopathy subtypes (Table 2).

Developing anticoagulation management strategies in patients with cardiomyopathy is associated with considerable challenges for several reasons. Besides the lack of data regarding thromboembolic events in cardiomyopathy, the pathogenesis of TE in certain cardiomyopathy subtypes largely remains unclear. AF seems to worsen this scenario by additionally increasing the risk of stroke and systemic embolism in this patient cohort that is more likely to develop AF than the general population. Furthermore, there is a lack of randomized controlled trials (RCTs) or large-scale data, including the choice of oral anticoagulation (OAC) regimen [vitamin K antagonist (VKA) vs. non-vitamin K oral anticoagulants]. Recognizing these limitations, management strategies should be individualized based on a thorough clinical evaluation, clinical experience, and evidence published so far.

The following overview will address the epidemiology and management for TE in cardiomyopathy subtypes.

**Hypertrophic cardiomyopathy**

**Epidemiology of thromboembolism in hypertrophic cardiomyopathy**

Hypertrophic cardiomyopathy depicts the most common monogenic cardiovascular disorder with morphological features of a hypertrophied, but non-dilated left ventricle.\textsuperscript{38,61} Former studies estimated the overall annual incidence of TE in patients with HCM as high as 0.8–1.3%, regardless of concomitant AF.\textsuperscript{31,48,49} However, observational study data reveal a frequency of AF ranging from 20% to 25% in HCM patients with a higher stroke risk if HCM is accompanied by AF.\textsuperscript{32,62} AF occurs in about a quarter of patients with HCM and LV outflow tract (LVOT) obstruction and has an annual incidence of 2–3%.\textsuperscript{32,62} This arrhythmia is poorly tolerated because the combination of the loss of the atrial contribution to ventricular filling and the rapid ventricular rate results in further elevations of LV diastolic pressure and symptoms of HF.\textsuperscript{32,62,63} It is also a major risk factor for thromboembolic stroke in patients with HCM.\textsuperscript{32,62,64}

**Anticoagulation management in hypertrophic cardiomyopathy**

Hypertrophic cardiomyopathy differs from other forms of LV hypertrophy due to its distinct pathophysiology. Hence, treatment strategies should take this into
consideration.\textsuperscript{65} Observational studies have revealed benefits of prophylactic anticoagulant therapy with warfarin for HCM patients with AF.\textsuperscript{7,32,35} Embolic stroke is the most important sequela of AF, supporting a low threshold for prophylaxis with oral anticoagulants (primary prophylaxis), instead of a reactive therapy approach (secondary prophylaxis) only if embolic events had happened.\textsuperscript{61} A recent study including 1558 consecutive HCM patients (20% had episodes of AF) revealed embolic events were less frequent with prophylactic anticoagulation (2%) than without (14%).\textsuperscript{66} However, no correlation could be established between CHA2DS2-VASc score and clinical outcomes in the setting of HCM so far.\textsuperscript{7,62} Although there is only rare evidence given by RCTs assessing the role of anticoagulation in this population, current guidelines strongly recommend anticoagulation for all patients with AF independent of CHA2DS2-VASc score in terms of a class I recommendation.\textsuperscript{32–34,62,65,66} Moreover, the European Society of Cardiology (ESC) recommends life-long OAC for HCM patients who have experienced a first episode of AF in order to prevent stroke (class I recommendation).\textsuperscript{7,32,62,68} Additionally, there is no RCT on the effectiveness of non-vitamin K antagonist oral anticoagulants (NOACs) in reducing thromboembolic risk in HCM patients with AF. Nevertheless, some data show that NOACs (i.e. rivaroxaban and dabigatran) might be safe and effective in this population.\textsuperscript{69–71}

Left ventricular apical aneurysms (LVAAs) in the context of HCM often result from apical scar tissue and muscular obstruction of the middle LV cavity. It is associated with a high risk of TE.\textsuperscript{43,72} Therefore, prophylactic anticoagulation is recommended for all HCM patients with LVAA irrespective of its size.\textsuperscript{41–43} In addition, in hypertrophic obstructive cardiomyopathy, permanent anticoagulant therapy might also be considered on an empirical basis in patients with an enlarged LA dimension (≥48 mm), regardless of the presence of AF.\textsuperscript{4,31}

### Dilated cardiomyopathy

#### Epidemiology of thromboembolism in dilated cardiomyopathy

Dilated cardiomyopathy is defined as a non-ischaemic heart muscle disease with LV or biventricular dilation and systolic dysfunction without hypertension, valvular disease, or congenital heart disease.\textsuperscript{1,73} A wide variation regarding the incidence of TE in patients with DCM can be found in literature.\textsuperscript{74} A post-mortem analysis of Roberts et al. reported a 37% frequency of thromboembolic events by reviewing 152 consecutive patients with DCM,\textsuperscript{75} whereas other investigators reported a lower occurrence rate of TE with an 18% and an annual incidence of 3.5%, if no anticoagulation regimen was applied.\textsuperscript{51} A previous study consisting of 45 DCM patients without AF or anticoagulant therapy has reported LAA thrombi in 68.9% and LV thrombi in 13.3%.\textsuperscript{76} Interestingly, a retrospective study reported only 3% frequency of arterial embolization by investigating 224 patients awaiting heart transplantation [mean left ventricular ejection fraction (LVEF) = 20%] over a mean follow-up period of 301 days.\textsuperscript{77} With regard to the prevalence of AF in DCM, some studies have revealed a frequency of AF ranging from 9.5% to 29.4% in patients with DCM,\textsuperscript{78,79} whereas no precise incidence data of TE and stroke in this population were available.

### Table 2 Mophsological feature, incidence of thromboembolism and stroke, and impact of AF in cardiomyopathy subtypes

| Cardiomyopathy subtype | Morphological feature | Incidence of TE | Prevalence of stroke | Relative risk of stroke/TE with vs. without AF |
|------------------------|-----------------------|-----------------|----------------------|-----------------------------------------------|
| HCM                    | LV hypertrophy without dilation | Annual incidence 0.8–1.3%\textsuperscript{31,48,49} | 3–5%\textsuperscript{9,48,50} | 8 times (21% vs. 2.6%)\textsuperscript{32} |
| DCM                    | LV or biventricular dilation with systolic dysfunction | Annual incidence 3.5%\textsuperscript{51} | 4.5%\textsuperscript{9} | N/A |
| RCM                    | Increased myocardial stiffness with impaired ventricular filling | N/A | 4.5%\textsuperscript{9} | N/A |
| CM                     | Increased biventricular wall thickness with restrictive LV filling, often without LV dilation | 7.6%\textsuperscript{52} | 5.2%\textsuperscript{52} | 2.2 times (10.6% vs. 4.9%)\textsuperscript{52} |
| HES                    | Increased myocardial stiffness and impaired ventricular filling together with sustained serum eosinophilia | 25%\textsuperscript{23,53} | 15%\textsuperscript{54} | N/A |
| ARVC                   | RV wall thinning and aneurysmal dilatation with dysfunction and risk of sudden cardiac death | 4%\textsuperscript{24,26,30} | N/A | N/A |
| LVNC                   | Prominent LV trabeculae with a thin compacted layer and deep intertrabecular recesses | 13–24%\textsuperscript{55–57} | N/A | N/A |
| TTS                    | Acute transient LV wall motion abnormality, often triggered by emotional or physical stress occurring during peripartum period | 2.2–12.2%\textsuperscript{16,58} | N/A | 1.7 times (5.4% vs. 3.2%)\textsuperscript{17} |
| PPCM                   | Systolic dysfunction (LVEF < 45%) with LVNC | 6.8–17%\textsuperscript{59,60} | N/A | N/A |

AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HES, hypereosinophilic syndrome; LV, left ventricular; LVEF, left ventricular ejection fraction; LVNC, left ventricular noncompaction; N/A, not applicable; RCM, restrictive cardiomyopathy; RV, right ventricular; TE, thromboembolism; TTS, Takotsubo syndrome.

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available in these studies. Nevertheless, the European Cardiomyopathy Registry reports a 4.5% rate of history of stroke in patients with DCM.\textsuperscript{9}

**Anticoagulation in dilated cardiomyopathy** Dilated cardiomyopathy secondary to LV systolic dysfunction remains one of the most common causes of non-ischaemic HF.\textsuperscript{80} This has led in the past to an interchangeable use of both terms.\textsuperscript{21,22,74,81} Concerning the role of anticoagulation, there is an ongoing controversy in HF patients with reduced LVEF. Earlier studies hypothesized that anticoagulant therapy is more effective than antiplatelet therapy for the prevention of TE in patients with DCM, especially with concomitant severe LV enlargement and dysfunction.\textsuperscript{27,74}

However, recent randomized clinical trials (WATCH and WAREF trials) revealed that among patients with reduced LVEF secondary to ischaemic HF or DCM and sinus rhythm, there is only a slight benefit of anticoagulant therapy with warfarin compared with antiplatelet therapy in terms of a decreased risk of ischaemic stroke, however, offset by increased risk of major haemorrhage.\textsuperscript{82,83} Therefore, OAC is not recommended for patients with DCM/HF who remain in sinus rhythm.\textsuperscript{84–86} However, anticoagulant therapy should be considered in patients with DCM/HF and a history of previous TE or LV thrombus.\textsuperscript{44,74} Additionally, most patients with DCM/HF and AF are potential candidates for OAC due to a CHA\textsubscript{2}DS\textsubscript{2}-VASc score $\geq 1$.\textsuperscript{65,87,88} Although there is more experience with VKA, no data show that NOACs cannot be used in these patients. In order to decrease the risk of bleeding rates and to improve anticoagulant therapy compliance, NOACs (dabigatran, rivaroxaban, etc.) are regarded as a promising alternative.\textsuperscript{21} However, currently, there is no consensus on the choice of anticoagulants in patients with DCM.\textsuperscript{7,78} Hence, the anticoagulant regimen should always be individualized in these patients.

In addition, inflammatory cardiomyopathy is defined as myocarditis associated with cardiac insufficiency and ventricular remodelling, which can present as an initially unexplained, usually dilated, cardiomyopathy.\textsuperscript{15,89,90} A recent definition of possible acute myocarditis was one of several clinical syndromes, including HF of $<3$ months’ duration, in association with other unexplained elevation in troponin or imaging features of cardiac injury. While there is a lack of data regarding incidence of TE and anticoagulation management in myocarditis,\textsuperscript{15} anticoagulation might be considered in myocarditis patients presenting as DCM/HF with a history of previous TE, an evident intracavitary thrombus, or paroxysmal/persistent AF with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score $\geq 1$.

**Restrictive cardiomyopathy**

**Epidemiology of thromboembolism in restrictive cardiomyopathy** Restrictive cardiomyopathy is characterized by an increased myocardial stiffness that results in impaired ventricular filling associated with near-normal to normal systolic function and biventricular chamber size. It depicts the least common of four major cardiomyopathy subtypes.\textsuperscript{9,91} Due to its diverse aetiology and regional prevalence,\textsuperscript{94} to date, an overall epidemiology of RCM including associated incidence of TE has not yet been well established. The European Cardiomyopathy Registry reported a 48.5% rate of history of AF and a 4.5% rate of history of stroke in patients with RCM.\textsuperscript{9}

**Anticoagulation in restrictive cardiomyopathy** Despite the heterogeneous nature of origin and presentation, there is an indication for anticoagulation in RCM patients with AF, history of intracardiac thrombus formation, or evidence of systemic embolization, on an empirical basis.\textsuperscript{91} While anticoagulation with warfarin was recommended for these patients in early literature,\textsuperscript{40} NOACs might be considered in NOAC-eligible patients. The European Cardiomyopathy Registry reported a 58.1% rate of anticoagulation therapy with oral anticoagulants (38.7% with VKA and 19.4% with NOACs as well as other anticoagulants) in RCM patients,\textsuperscript{9} but there was a lack of outcome data regarding anticoagulation in these patients. Particular concern will be put on cardiac amyloidosis (CA) and HES, two of the most common RCMs associated with TE.

**Cardiac amyloidosis**

**Epidemiology of thromboembolism in cardiac amyloidosis** Cardiac amyloidosis is an infiltrative cardiomyopathy characterized by cardiac amyloid deposition causing increased biventricular wall thickness, restrictive LV filling, and often without LV dilation.\textsuperscript{15,92} It is associated with a high prevalence of intracardiac thrombosis (18–35%), especially in patients with AF and primary amyloidosis (amyloid light chain, AL type).\textsuperscript{93,94} However, a retrospective cohort study of 100 patients with transthyretin amyloidosis (ATTR) and AF revealed no association between the presence of LAA thrombus disclosed by TEE and the CHA\textsubscript{2}DS\textsubscript{2}-VASc score.\textsuperscript{95} In addition, a latest study investigating the occurrence of arterial thromboembolic events in 406 consecutive CA patients reported 31 patients (7.6%) suffered from an arterial thromboembolic event, including 21 patients (5.2%) with ischaemic stroke. Furthermore, the patients with AF in this CA cohort had higher incidence rate of TE compared with the patients in sinus rhythm.\textsuperscript{52}

**Anticoagulation in cardiac amyloidosis** Previous studies have reported a high prevalence of intracardiac thrombosis in CA patients, especially with AF and AL type amyloidosis. However, the potential benefit of anticoagulant therapy has to be carefully weighed up against the increased risk of major haemorrhage in patients with vasculopathy secondary to amyloid deposition. However, anticoagulation with either VKA or NOACs can usually be safely prescribed to CA patients.\textsuperscript{96,97} The American Heart Association (AHA) recommends anticoagulation (warfarin therapy with a target
international normalized ratio of 2 to 3 or direct thrombin inhibitors) for CA patients with concomitant AF or history of thromboembolic stroke/TIA (transient ischaemic attack) in terms of a class I recommendation due to the high risk of intracardiac clot formation, even in the presence of sinus rhythm as both atria often present as ‘standstill’ secondary to amyloid infiltration. 15,94 On an empirical basis, anticoagulation is also recommended in patients with demonstrable atrial or ventricular clot. 15,94

Hypereosinophilic syndrome

Epidemiology of thromboembolism in hypereosinophilic syndrome Hypereosinophilic syndrome, also known as Loeffler’s endocarditis or eosinophilic myocarditis (EM), depicts a life-threatening disease most frequent in tropical and subtropical regions. 15,54 It generally presents as RCM together with sustained serum eosinophilia (>1500/µL) for 1 to 6 months or longer 54,98 and shows a pathophysiological evolution through the stages of necrosis, thrombosis, and fibrosis. 15,99 It is reported that approximately one-quarter of patients with HES develop TE and that 5–10% die of embolic complications. 23,53 In addition, an analysis of 26 case reports of Loeffler’s endocarditis showed 15% rate of symptomatic stroke. 54 Nevertheless, there was a paucity of data regarding AF and TE in this population.

Anticoagulation in hypereosinophilic syndrome

Eosinophilic myocarditis is one of the leading causes of morbidity and mortality in patients with HES. It differs from other cardiomyopathies as thrombus formation per se depicts one of the three stages of eosinophilic heart disease pathology. 23 Nevertheless, there is an ongoing controversy regarding the role of systemic anticoagulation in EM patients with documented atrial or ventricular clot. Currently, anticoagulation is reasonable in EM patients who have experienced a prior embolic event 39,40,98 and might be as well considered in patients with documented intracardiac clot. However, as treatment failure is common in EM and anticoagulation per se has no impact on the progression of HES, supporting evidence for routine OAC is missing. 23,53,98 Prophylactic anticoagulation should be administered on an individually and carefully weighed basis only. In addition, most of the literature shows that warfarin is the main anticoagulant regimen, and NOACs have not been significantly used in these patients. 54,100

Arrhythmogenic right ventricular cardiomyopathy

Epidemiology of thromboembolism in arrhythmogenic right ventricular cardiomyopathy Arrhythmogenic right ventricular cardiomyopathy, also known as arrhythmogenic cardiomyopathy or arrhythmogenic right ventricular dysplasia, belongs to the inherited heart muscle disorders and is characterized by ventricular arrhythmias with a consecutively high risk of sudden cardiac death. It predominantly affects the right ventricle with a progressive loss of myocytes, being replaced by fibrofatty tissue, and resulting in wall thinning and aneurysmal dilatation. 6,101,102 ARVC is associated with a risk of developing intracardiac thrombi, especially in patients with right ventricular dilation, aneurysms, and wall motion abnormalities. 103 Published data indicated an incidence rate of TE as high as 4% in ARVC. 26,30 In a retrospective cohort study, 13 of 467 (2.8%) patients with ARVC developed a right ventricular thrombus during follow-up. However, the precise incidence rate of TE in ARVC cases with AF is not known due to the rarity of this setting and the impact of reporting bias. 24

Anticoagulation in arrhythmogenic right ventricular cardiomyopathy

A retrospective study consisting of 126 ARVC patients with severe right ventricular dilatation has revealed a significantly lower annual incidence of TE compared with patients with LV failure. 26 As such, prophylactic anticoagulation is not recommended in ARVC patients with ventricular dilatation for primary prevention of TE, irrespective of the extent of ventricular dysfunction. 26,104 However, long-term OAC is indicated in ARVC patients with documented intracardiac thrombus or systemic TE in terms of secondary prevention. 104 A retrospective study consisting of 13 ARVC patients with a right ventricular thrombus showed that therapeutic anticoagulation (warfarin, rivaroxaban, or apixaban) was effective, resulting in complete thrombus resolution in most cases (69%). 24 Moreover, it suggested that warfarin might be as effective as NOACs in patients with ARVC. 24 Therefore, it is difficult to derive any recommendations for the choice of anticoagulation regimen because further studies are warranted to evaluate the efficacy of NOACs in these patients. Despite the paucity of data regarding anticoagulation in ARVC with AF, OAC therapy might be considered on an empirical basis in ARVC patients with documented AF. 6

Other cardiomyopathy subtypes

Left ventricular noncompaction/cardiomyopathy

Epidemiology of thromboembolism in left ventricular noncompaction Left ventricular noncompaction, also known as LV hypertrabeculation, depicts a rare cardiomyopathy characterized by prominent LV trabeculae with a thin compacted layer and deep intertrabecular recesses. 105 It is frequently associated with arrhythmia, HF, or TE. 106,107 The frequency of TE varies widely in adult and paediatric patients with 13–24% 55–57 and 0–38% 108 respectively. No precise incidence data regarding AF and TE are available due to the rarity of this disease. A retrospective study investigating the TE event rate in 45 patients with left ventricular noncompaction (LVNC) reported three thromboembolic episodes in two patients (4%), both of whom were in absence of AF during 10 years of follow-up, whereas no TE events occurred in the only three LVNC patients with AF. 109
Anticoagulation in left ventricular noncompaction

Notwithstanding big disparities regarding the frequencies of TE in LVNC in previous studies, cardioembolic stroke or embolism appears to be not common in LVNC patients with normal LVEF and sinus rhythm.56,110 Hence, routine OAC is recommended only for adult LVNC patients with concomitant risk factors for TE as LVEF < 40%, AF, history of previous embolism, or documented intracavitary thrombus.56,106,110 Otherwise, prophylactic anticoagulation is not indicated neither in adult nor in paediatric LVNC patients, especially in the presence of normal systolic function, as it harbours the risk of iatrogenic major haemorrhage with otherwise low risk of TE.110–114 For OAC in LVNC patients with LV thrombi, a latest multicentre cohort study revealed that VKA seemed to be more effective than NOACs,115 which implied VKA might be preferred in these patients.116 However, to date, there are no patients with LVNC and AF included in trials comparing warfarin with NOACs; thus, the choice of OAC therapy should be built on an individual basis.

Takotsubo syndrome

Epidemiology of thromboembolism in Takotsubo syndrome Takotsubo syndrome, also described as ‘stress cardiomyopathy’, ‘broken heart syndrome’, or ‘apical ballooning syndrome’, is characterized by an acute transient wall motion abnormality of the left ventricle, often triggered by emotional or physical stress with consecutive catecholamines surge.15,117,118 It shares clinical features with acute coronary syndrome and hence depicts an important differential diagnosis of acute chest pain.15,118 Thromboembolic complications occur in 2.2–12.2% of all cases.16,58 A recently published study consisting of 1676 TTS patients has reported intraventricular thrombi and/or embolism in 3.3% of all patients up to Day 38 after TTS diagnosis was established, occurring in 5.4% of patients with AF and 3.2% of patients with a sinus rhythm.17

Anticoagulation in Takotsubo syndrome According to main involved segments in TTS identified by echocardiography, the following four phenotypes can be distinguished: apical (ballooning), midventricular, basal, and focal.119 Conflicting data have been published regarding the correlation of TTS variant and incidence of ventricular derived TE. Santoro et al. revealed that incidence of LV thrombi depend on TTS variants.16 However, El-Battrawy et al. reported that the type of TTS was not related to the thromboembolic events.120 Currently, therapeutic anticoagulation with heparin, alternatively also with VKA and NOACs, respectively, is recommended for TTS patients with LV thrombosis or embolization until first follow-up to reduce the risk of systemic embolism.119,121 Anticoagulation should also be considered in patients with an LVEF ≤ 30%, or in case of a pronounced LV dysfunction involving the apex. Post-discharge OAC might be considered on an individual case-by-case basis.119,121 Prophylactic anticoagulation is not recommended for TTS patients with otherwise low risk of TE (e.g. normal or near-normal LVEF and elevated troponin level).16 In addition, no specific association between prophylactic anticoagulation and outcome in TTS patients with AF had been established in previous studies.

Peripartum cardiomyopathy

Epidemiology of thromboembolism in peripartum cardiomyopathy Peripartum cardiomyopathy is defined as an idiopathic cardiomyopathy with reduced LVEF (<45%) occurring towards the end of pregnancy up to 5 months after delivery, in the absence of any other causes for HF.15,18 A previous study revealed an even higher rate of LV thrombi (17%) in patients with PPCM than in patients with DCM.59 In addition, the PPCM worldwide registry reports an incidence of 6.8% of peripheral arterial and venous embolism in the first month post-partum, whereas no incidence data regarding AF and TE/stroke are reported in this population.60

Anticoagulation in peripartum cardiomyopathy Despite the lack of published data to direct the decision of therapeutic versus prophylactic anticoagulation, prophylactic anticoagulation is considered reasonable in patients with severely decreased LVEF due to the hypercoagulability with its consecutive risk of TE during pregnancy and early post-partum phase.122,123 However, controversy has arisen regarding the cut-off value of decreased LVEF for anticoagulant indication in these patients: the AHA recommends anticoagulation for PPCM patients with reduced LVEF below 30%,15 whereas it is recommended by the Heart Failure Association (HFA) of the ESC Study Group on PPCM, if LVEF decreases below 35%.124 Due to a high incidence of venous and systemic embolism during pregnancy as well as the early period after delivery, especially in the first 30 days post-partum, the HFA of the ESC Study Group on PPCM recommends anticoagulation with low molecular weight heparin (LMWH) or OAC at least in prophylactic dose in PPCM patients with reduced LVEF (<45%).18,28,60 As the use of mainly high-dose bromocriptine is associated with thromboembolic events, anticoagulation with heparin at least in prophylactic dose should be administered in PPCM patients treated with bromocriptine.18,29,125 In addition, the HFA of the ESC Study Group on PPCM highly recommends therapeutic anticoagulation in patients who have at least one of the following complications: documented intracavitary thrombi, evidence of systemic embolism, or AF.18

Of particular note, anticoagulant therapy always needs to pay attention to medication safety during pregnancy and lactation.18 Generally, NOACs should not be administered for PPCM patients during pregnancy and lactation; VKA should be avoided during the first trimester.18,126,127 LMWH has to be used with caution in patients during pregnancy and lactation,18,126,128,129 and VKA in patients during lactation.18,123,130 VKA might be considered with extreme
Table 3  Current recommendations for anticoagulation management in cardiomyopathy subtypes with atrial fibrillation and other comorbidities related to thromboembolism

| Concomitant AF | Enlarged LAD | Previous TE/evident intracavitary thrombus | Ventricular dilatation/dysfunction, LVAA | Using bromocriptine |
|----------------|-------------|---------------------------------------------|----------------------------------------|---------------------|
| HCM            | OAC recommended | OAC considered in obstructive HCM with LAD ≥ 48 mm | — | OAC suggested in HCM with LVAA |
| DCM            | OAC recommended as CHA2DS2-VASc score ≥ 1 | — | Anticoagulant therapy suggested | — |
| RCM            | OAC suggested | — | OAC suggested | — |
| CM             | VKA or direct thrombin inhibitors recommended | — | VKA or direct thrombin inhibitors recommended | — |
| HES            | — | — | VKA recommended | — |
| ARVC           | OAC considered | — | OAC recommended | — |
| LVNC           | VKA preferred | — | VKA preferred | VKA preferred as LVEF < 40% |
| TTS            | — | Heparin (intravenous/subcutaneous)/VKA/NOACs recommended | Heparin/VKA/NOACs considered if LVEF ≤ 30%, or large LVD involving apex | — |
| PPCM           | LMWH recommended; VKA might be considered during lactation or during the second/third trimester | — | LMWH recommended; VKA might be considered during lactation or during the second/third trimester | Heparin recommended |

LMWH, low molecular weight heparin; LVAA, left ventricular apical aneurysm; LVD, left ventricular dysfunction; NOACs, non-vitamin K oral anticoagulants; OAC, oral anticoagulation; VKA, vitamin K antagonist.
Anticoagulation in cardiomyopathy

Table 4 The direction for future research in the field of anticoagulation therapy in cardiomyopathy

| The future research priorities in anticoagulation therapy in cardiomyopathy |
|---|
| Investigate the epidemiology of intracardiac thrombus, stroke, or other embolic events, respectively, for various cardiomyopathy subtype. | |
| Evaluate the epidemiology of thromboembolic events with or without AF in collaborative studies, to further elucidate underlying pathophysiological mechanisms. | |
| Develop markers as ‘risk reporters’ among ‘high-risk patients with cardiomyopathy’, including clinical and advanced technology variable. | |
| Conduct adequately powered clinical trials, on effectiveness and safety with existing anticoagulation strategies (VKA vs. NOACs). | |
| Conduct exploratory trials using data available and expert opinion based on weighing the benefit of anticoagulation against the potential increased risk of bleeding, to establish the optimal duration of anticoagulation therapy. | |
| Conduct evidence-based management guidelines for anticoagulation therapy in cardiomyopathy subtypes. | |
| AF, atrial fibrillation; NOACs, non-vitamin K oral anticoagulants; VKA, vitamin K antagonist. | |

Conclusions and future directions

Patients with cardiomyopathy are evidently more likely to develop TE than the general population. However, data available do not unequivocally support anticoagulation therapy in all of these patients, especially in patients with a low risk of TE. Due to the lack of precise data regarding TE incidence in cardiomyopathies and co-existence of AF and other comorbidities, together with RCTs regarding OAC in this population, developing optimal anticoagulation management in these patients remains considerable challenges, including the decision of therapeutic versus prophylactic anticoagulation, the choice of anticoagulation regimen, and so on. Given that current recommendations are mostly based on small-sample studies or empirical evidence, management strategies should be individualized based on a thorough clinical evaluation, clinical experience, and evidence published so far. The future research priorities in this area, outlined in Table 4, will help to facilitate the development of evidence-based risk assessment and guideline-directed management and therapy.

Conflict of interest

The authors declare no conflicts of interest.

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