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REVIEW

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 CHA_2DS_2-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

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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.[1] 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.[2–8] 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%.[9] 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.[16,23–25] Ventricular dilatation and dysfunction, as seen in dilated cardiomyopathy (DCM) as well as catecholamine surges in TTS 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.[45] Thibodeau and Drazner give an informative summary regarding the role of clinical examination in determining haemodynamic state and prognosis of the patient.[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.[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,[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.[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.[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.[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%.[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.[32,62,63] It is also a major risk factor for thromboembolic stroke in patients with HCM.[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

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Table 2 Morphological 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 of 0.8–1.3%[31,48,49]	3–5%[9,48,50]	8 times (21% vs. 2.6%)[32]
DCM	LV or biventricular dilation with systolic dysfunction	Annual incidence of 3.5%[51]	4.5%[9]	N/A
RCM	Increased myocardial stiffness with impaired ventricular filling	N/A	4.5%[9]	N/A
CM	Increased biventricular wall thickness with restrictive LV filling, often without LV dilation	7.6%[52]	5.2%[52]	2.2 times (10.6% vs. 4.9%)[52]
HES	Increased myocardial stiffness and impaired ventricular filling together with sustained serum eosinophilia	25%[23,53]	15%[54]	N/A
ARVC	RV wall thinning and aneurysmal dilatation with dysfunction and risk of sudden cardiac death	4%[24,26,30]	N/A	N/A
LVNC	Prominent LV trabeculae with a thin compacted layer and deep intertrabecular recesses	13–24%[55–57]	N/A	N/A
TTS	Acute transient LV wall motion abnormality, often triggered by emotional or physical stress	2.2–12.2%[16,58]	N/A	1.7 times (5.4% vs. 3.2%)[17]
PPCM	Systolic dysfunction (LVEF $<$ 45%) occurring during peripartum period	6.8–17%[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.

consideration.[65] Observational studies have revealed benefits of prophylactic anticoagulant therapy with warfarin for HCM patients with AF.[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.[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%).[66] However, no correlation could be established between CHA_2DS_2-VASc score and clinical outcomes in the setting of HCM so far.[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 HCM and AF independent of CHA_2DS_2-VASc score in terms of a class I recommendation.[32–34,62,65,67] 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).[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.[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.[43,72] Therefore, prophylactic anticoagulation is recommended for all HCM patients with LVAA irrespective of its size.[41–43] In addition, in hypertrophic obstructive cardiomyopathy, permanent anticoagulant therapy might be considered on an empirical basis in patients with an enlarged LA dimension (≥48 mm), regardless of the presence of AF.[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.[1,73] A wide variation regarding the incidence of TE in patients with DCM can be found in literature.[74] A post-mortem analysis of Roberts *et al*. reported a 37% frequency of thromboembolic events by reviewing 152 consecutive patients with DCM,[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.[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%.[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.[77] With regard to the prevalence of AF in DCM, some study revealed a frequency of AF ranging from 9.5% to 29.4% in patients with DCM,[78,79] whereas no precise incidence data of TE and stroke in this population were

available in these studies. Nevertheless, the European Cardiomyopathy Registry reports a 4.5% rate of history of stroke in patients with DCM.[9]

Anticoagulation in dilated cardiomyopathy Dilated cardiomyopathy secondary to LV systolic dysfunction remains one of the most common causes of non-ischaemic HF.[80] This has led in the past to an interchangeable use of both terms.[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.[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.[82,83] Therefore, OAC is not recommended for patients with DCM/HF who remain in sinus rhythm.[84–86] However, anticoagulant therapy should be considered in patients with DCM/HF and a history of previous TE or LV thrombus.[44,74] Additionally, most patients with DCM/HF and AF are potential candidates for OAC due to a CHA_2DS_2-VASc score ≥ 1.[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.[21] However, currently, there is no consensus on the choice of anticoagulants in patients with DCM.[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.[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,[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_2DS_2-VASc score ≥ 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.[9,91] Due to its diverse aetiology and regional prevalence,[91] 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.[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.[91] While anticoagulation with warfarin was recommended for these patients in early literature,[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,[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.[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).[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_2DS_2-VASc score.[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.[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.[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 $\leq$ 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 $\geq$ 48 mm	—	OAC suggested in HCM with LVAA	—
DCM	OAC recommended as CHA_2DS_2-VASc score $\geq$ 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 $\leq$ 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	LMWH suggested if LVEF $<$ 45%; 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.

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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
Construct evidence-based management guidelines for anticoagulation therapy in cardiomyopathy subtypes

AF, atrial fibrillation; NOACs, non-vitamin K oral anticoagulants; VKA, vitamin K antagonist.

caution in PPCM patients during the second or third trimester, however, only in cases with compelling indications such as mechanical valves.[18,123,126]

Table 3 aims to summarize current published proposals for anticoagulation regimens in various cardiomyopathy subtypes with or without AF. It might help to guide clinicians to select the optimal treatment strategy for each patient individually.

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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References

1. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kühl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008; **29**: 270–276.
2. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB, American Heart Association, Council on Clinical Cardiology, Heart Failure and Transplantation Committee, Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups, Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology Heart Failure and Transplantation Committee Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups and Council on Epidemiology and Prevention. *Circulation* 2006; **113**:1807–1816.
3. Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. *Lancet* 2017; **390**: 400–414.
4. Veselka J, Anavekar NS, Charron P. Hypertrophic obstructive cardiomyopathy. *Lancet* 2017; **389**: 1253–1267.
5. Pereira NL, Grogan M, Dec GW. Spectrum of Restrictive and Infiltrative Cardiomyo-pathies: Part 1 of a 2-Part Series. *J Am Coll Cardiol* 2018; **71**: 1130–1148.
6. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med* 2017; **376**: 1489–1490.
7. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and

Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014; **35**: 2733–2779.
8. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, Duboc D, Gimeno J, de Groote P, Imazio M, Heymans S, Klingel K, Komajda M, Limongelli G, Linhart A, Mogensen J, Moon J, Pieper PG, Seferovic PM, Schueler S, Zamorano JL, Caforio AL, Charron P. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J* 2016; **37**: 1850–1858.
9. Charron P, Elliott PM, Gimeno JR, Caforio ALP, Kaski JP, Tavazzi L, Tendera M, Maupain C, Laroche C, Rubis P, Jurcut R, Calò L, Heliö TM, Sinagra G, Zdravkovic M, Kavoliuniene A, Felix SB, Grzybowski J, Losi MA, Asselbergs FW, García-Pinilla JM, Salazar-Mendiguchia J, Mizia-Stec K, Maggioni AP, EORP Cardiomyopathy Registry Investigators. The cardiomyopathy registry of the EURObservational research programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. *Eur Heart J* 2018; **39**: 1784–1793.
10. Ntaios G, Perlepe K, Lambrou D, Sirimarco G, Strambo D, Eskandari A, Karagkiozi E, Vemmou A, Koroboki E, Manios E, Makaritsis K, Vemmos K, Michel P. Prevalence and overlap of potential embolic sources in patients with embolic stroke of undetermined source. *J Am Heart Assoc* 2019; **8**: e012858.
11. Ntaios G. Embolic stroke of undetermined source: JACC review topic of the week. *J Am Coll Cardiol* 2020; **75**: 333–340.
12. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol* 1999; **33**: 1424–1426.
13. Ntaios G, Vemmos K, Lip GY. Oral anticoagulation versus antiplatelet or placebo for stroke prevention in patients with heart failure and sinus rhythm: Systematic review and meta-analysis of randomized controlled trials. *Int J Stroke* 2019; **14**: 856–861.
14. Kamel H, Longstreth WT Jr, Tirschwell DL, Kronmal RA, Broderick JP, Palesch YY, Meinzer C, Dillon C, Ewing I, Spilker JA, Di Tullio MR, Hod EA, Soliman EZ, Chaturvedi S, Moy CS, Janis S, Elkind MS. The AtRial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke randomized trial: rationale and methods. *Int J Stroke* 2019; **14**: 207–214.
15. Bozkurt B, Colvin M, Cook J, Cooper LT, Deswal A, Fonarow GC, Francis GS, Lenihan D, Lewis EF, McNamara DM, Pahl E, Vasan RS, Ramasubbu K, Rasmusson K, Towbin JA, Yancy C, American Heart Association Committee on Heart Failure and Transplantation of the Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Quality of Care and Outcomes Research. Current diagnostic and treatment strategies for specific dilated cardiomyopathies. *Circulation* 2016; **134**: e579–e646.
16. Santoro F, Stiermaier T, Tarantino N, De Gennaro L, Moeller C, Guastafierro F, Marchetti MF, Montisci R, Carapelle E, Graf T, Caldarola P, Thiele H, Di Biase M, Brunetti ND, Eitel I. Left ventricular thrombi in Takotsubo Syndrome: incidence, predictors, and management: results from the GEIST (German Italian Stress Cardiomyopathy) registry. *J Am Heart Assoc* 2017; **6**: e006990.
17. Ding KJ, Cammann VL, Szawan KA, Stähli BE, Wischnewsky M, Di Vece D, Citro R, Jaguszewski M, Seifert B, Sarcon A, Knorr M, Heiner S, Gili S, D'Ascenzo F, Neuhaus M, Napp LC, Franke J, Noutsias M, Burgdorf C, Koenig W, Kherad B, Rajan L, Michels G, Pfister R, Cuneo A, Jacobshagen C, Karakas M, Pott A, Meyer P, Arroja JD, Banning A, Cuculi F, Kobza R, Fischer TA, Vasankari T, Airaksinen KEJ, Paolini C, Bilato C, Carrilho-Ferreira P, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Dichtl W, Chan C, Bridgman P, Delmas C, Lairez O, El-Battrawy I, Akin I, Gilyarova E, Shilova A, Gilyarov M, Kozel M, Tousek P, Widimský P, Winchester DE, Galuszka J, Ukena C, Horowitz JD, Di Mario C, Prasad A, Rihal CS, Pinto FJ, Crea F, Borggrefe M, Braun-Dullaeus RC, Rottbauer W, Bauersachs J, Katus HA, Hasenfuß G, Tschöpe C, Pieske BM, Thiele H, Schunkert H, Böhm M, Felix SB, Münzel T, Bax JJ, Lüscher TF, Ruschitzka F, Ghadri JR, Bossone E, Templin C. Intraventricular thrombus formation and embolism in Takotsubo syndrome: insights from the international Takotsubo registry. *Arterioscler Thromb Vasc Biol* 2020; **40**: 279–287.
18. Bauersachs J, König T, van der Meer P, Petrie MC, Hilfiker-Kleiner D, Mbakwem A, Hamdan R, Jackson AM, Forsyth P, de Boer RA, Mueller C, Lyon AR, Lund LH, Piepoli MF, Heymans S, Chioncel O, Anker SD, Ponikowski P, Seferovic PM, Johnson MR, Mebazaa A, Sliwa K. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2019; **21**: 827–843.
19. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, Amlie J, Carlsen J. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; **358**: 2678–2687.
20. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Janosi A, Kamensky G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; **357**: 2248–2261.
21. Mischie AN, Chioncel V, Droc I, Sinescu C. Anticoagulation in patients with dilated cardiomyopathy, low ejection fraction, and sinus rhythm: back to the drawing board. *Cardiovasc Ther* 2013; **31**: 298–302.
22. Sirajuddin RA, Miller AB, Geraci SA. Anticoagulation in patients with dilated cardiomyopathy and sinus rhythm: a critical literature review. *J Card Fail* 2002; **8**: 48–53.
23. Mankad R, Bonnichsen C, Mankad S. Hypereosinophilic syndrome: cardiac diagnosis and management. *Heart* 2016; **102**: 100–106.
24. Akdis D, Chen K, Saguner AM, Stämpfli SF, Chen X, Chen L, Rao M, Haegeli LM, Tanner FC, Brunckhorst C, Song J, Duru F. Clinical characteristics of patients with a right ventricular thrombus in arrhythmogenic right ventricular cardiomyopathy. *Thromb Haemost* 2019; **119**: 1373–1378.
25. Persson R, Earley A, Garlitski AC, Balk EM, Uhlig K. Adverse events following implantable cardioverter defibrillator implantation: a systematic review. *J Interv Card Electrophysiol* 2014; **40**: 191–205.
26. Wlodarska EK, Wozniak O, Konka M, Rydlewska-Sadowska W, Biederman A, Hoffman P. Thromboembolic complications in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Europace* 2006; **8**: 596–600.
27. Yamamoto K, Ikeda U, Furuhashi K, Irokawa M, Nakayama T, Shimada K. The coagulation system is activated in idiopathic cardiomyopathy. *J Am Coll Cardiol* 1995; **25**: 1634–1640.
28. Brenner B. Haemostatic changes in pregnancy. *Thromb Res* 2004; **114**: 409–414.
29. Hilfiker-Kleiner D, Haghikia A, Berliner D, Vogel-Claussen J, Schwab J, Franke A, Schwarzkopf M, Ehlermann P, Pfister R, Michels G, Westenfeld R, Stangl V, Kindermann I, Kühl U, Angermann CE, Schlitt A, Fischer D, Podewski E, Böhm M, Sliwa K, Bauersachs J. Bromocriptine for the treatment of peripartum

cardiomyopathy: a multicentre randomized study. *Eur Heart J* 2017; **38**: 2671–2679.
30. Wu L, Yao Y, Chen G, Fan X, Zheng L, Ding L, Zhang S. Intracardiac thrombosis in patients with arrhythmogenic right ventricular cardiomyopathy. *J Cardiovasc Electrophysiol* 2014; **25**: 1359–1362.
31. Haruki S, Minami Y, Hagiwara N. Stroke and embolic events in hypertrophic cardiomyopathy: risk stratification in patients without atrial fibrillation. *Stroke* 2016; **47**: 936–942.
32. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001; **104**: 2517–2524.
33. Higashikawa M, Nakamura Y, Yoshida M, Kinoshita M. Incidence of ischemic strokes in hypertrophic cardiomyopathy is markedly increased if complicated by atrial fibrillation. *Jpn Circ J* 1997; **61**: 673–681.
34. Savage DD, Seides SF, Maron BJ, Myers DJ, Epstein SE. Prevalence of arrhythmias during 24-hour electrocardiographic monitoring and exercise testing in patients with obstructive and nonobstructive hypertrophic cardiomyopathy. *Circulation* 1979; **59**: 866–875.
35. Guttmann OP, Pavlou M, O'Mahony C, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, Garcia-Pavia P, McKenna WJ, Omar RZ, Elliott PM, Hypertrophic Cardiomyopathy Outcomes Investigators. Prediction of thrombo-embolic risk in patients with hypertrophic cardiomyopathy (HCM Risk-CVA). *Eur J Heart Fail* 2015; **17**: 837–845.
36. Chawla D, Jahangir A, Cooley R, Sra J, Tajik AJ. Isolated left atrial standstill in patients with hypertrophic cardiomyopathy and atrial fibrillation after restoration of sinus ehythm. *J Am Soc Echocardiogr* 2019; **32**: 1369–1372.
37. John RM, Kumar S. Sinus node and atrial arrhythmias. *Circulation* 2016; **133**: 1892–1900.
38. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. *J Am Coll Cardiol* 2014; **64**: 83–99.
39. Gottdiener JS, Maron BJ, Schooley RT, Harley JB, Roberts WC, Fauci AS. Two-dimensional echocardiographic assessment of the idiopathic hypereosinophilic syndrome: anatomic basis of mitral regurgitation and peripheral embolization. *Circulation* 1983; **67**:572–578.
40. Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. *N Engl J Med* 1997; **336**: 267–276.
41. Shenoy C, Maron MS. Hypertrophic cardiomyopathy with left ventricular apical aneurysm in brothers. *Am J Cardiol* 2011; **108**: 612–613.
42. Holloway CJ, Betts TR, Neubauer S, Myerson SG. Hypertrophic cardiomyopathy complicated by large apical aneurysm and thrombus, presenting as ventricular tachycardia. *J Am Coll Cardiol* 2010; **56**: 1961.
43. Rowin EJ, Maron BJ, Haas TS, Garberich RF, Wang W, Link MS, Maron MS. Hypertrophic cardiomyopathy with left ventricular apical aneurysm: implications for risk stratification and management. *J Am Coll Cardiol* 2017; **69**: 761–773.
44. Vaitkus PT, Barnathan ES. Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: a meta-analysis. *J Am Coll Cardiol* 1993; **22**: 1004–1009.
45. Thibodeau JT, Drazner MH. The role of the clinical examination in patients with heart failure. *JACC Heart Fail* 2018; **6**: 543–551.
46. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF, Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001; **344**: 1411–1420.
47. Manning WJ, Silverman DI, Keighley CS, Oettgen P, Douglas PS. Transesophageal echocardiographically facilitated early cardioversion from atrial fibrillation using short-term anticoagulation: final results of a prospective 4.5-year study. *J Am Coll Cardiol* 1995; **25**: 1354–1361.
48. Maron BJ, Olivotto I, Bellone P, Conte MR, Cecchi F, Flygenring BP, Casey SA, Gohman TE, Bongioanni S, Spirito P. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002; **39**: 301–307.
49. Furlan AJ, Craciun AR, Raju NR, Hart N. Cerebrovascular complications associated with idiopathic hypertrophic subaortic stenosis. *Stroke* 1984; **15**: 282–284.
50. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, Caleshu CA, Helms AS, Colan SD, Girolami F, Cecchi F, Seidman CE, Sajeev G, Signorovitch J, Green EM, Olivotto I. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation* 2018; **138**: 1387–1398.
51. Fuster V, Gersh BJ, Guiliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981; **47**: 525–531.
52. Cappelli F, Tini G, Russo D, Emdin M, Del Franco A, Vergaro G, Di Bella G, Mazzeo A, Canepa M, Volpe M, Perfetto F, Autore C, Di Mario C, Rapezzi C, Musumeci MB. Arterial thrombo-embolic events in cardiac amyloidosis: a look beyond atrial fibrillation. *Amyloid* 2021; **28**: 12–18.
53. Ogbogu P, Rosing DR, Horne MK. Cardiovascular manifestations of hypereosinophilic syndromes. *Immunol Allergy Clin North Am.* 2007; **27**: 457–475.
54. Kariyanna PT, Hossain NA, Onkaramurthy NJ, Jayarangaiah A, Hossain NA, Jayarangaiah A, McFarlane IM. Hypereosinophilia and Löffler's Endocarditis: a systematic review. *Am J Med Case Rep* 2021; **9**: 241–248.
55. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. *J Am Coll Cardiol* 2000; **36**: 493–500.
56. Stöllberger C, Blazek G, Dobias C, Hanafin A, Wegner C, Finsterer J. Frequency of stroke and embolism in left ventricular hypertrabeculation/noncompaction. *Am J Cardiol* 2011; **108**: 1021–1023.
57. Stöllberger C, Wegner C, Finsterer J. CHADS2- and CHA2DS2VASc scores and embolic risk in left ventricular hypertrabeculation/noncompaction. *J Stroke Cerebrovasc Dis* 2013; **22**: 709–712.
58. El-Battrawy I, Behnes M, Hillenbrand D, Haghi D, Hoffmann U, Papavassiliu T, Lang S, Fastner C, Becher T, Baumann S, Heggemann F, Kuschyk J, Borggrefe M, Akin I. Prevalence, clinical characteristics, and predictors of patients with thromboembolic events in takotsubo cardiomyopathy. *Clin Med Insights Cardiol* 2016; **10**: 117–122.
59. Amos AM, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. *Am Heart J* 2006; **152**: 509–513.
60. Sliwa K, Mebazaa A, Hilfiker-Kleiner D, Petrie MC, Maggioni AP, Laroche C, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van der Meer P, Roos-Hesselink JW, Seferovic P, van Spandonck-Zwarts K, Mbakwem A, Bohm M, Mouquet F, Pieske B, Hall R, Ponikowski P, Bauersachs J. Clinical characteristics of patients from the worldwide registry on peripartum cardiomyopathy (PPCM): EURObservational Research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on PPCM. *Eur J Heart Fail* 2017; **19**: 1131–1141.
61. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. *N Engl J Med* 2018; **379**: 655–668.
62. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial

fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart* 2014; **100**: 465–472.
63. Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res* 2017; **121**: 749–770.
64. Debonnaire P, Joyce E, Hiemstra Y, Mertens BJ, Atsma DE, Schalij MJ, Bax JJ, Delgado V, Marsan NA. Left atrial size and function in hypertrophic cardiomyopathy patients and risk of new-onset atrial fibrillation. *Circ Arrhythm Electrophysiol* 2017; **10**: e004052.
65. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; **64**: e1–e76.
66. Rowin EJ, Hausvater A, Link MS, Abt P, Gionfriddo W, Wang W, Rastegar H, Estes NAM, Maron MS, Maron BJ. Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation* 2017; **136**: 2420–2436.
67. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the heart rhythm society. *J Am Coll Cardiol* 2019; **74**: 104–132.
68. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; **37**: 2893–2962.
69. Camm CF, Camm AJ. Atrial fibrillation and anticoagulation in hypertrophic cardiomyopathy. *Arrhythm Electrophysiol Rev* 2017; **6**: 63–68.
70. Jung H, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, Lip GYH. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation with hypertrophic cardiomyopathy: a nationwide cohort study. *Chest* 2019; **155**: 354–363.
71. He S, Wang Z, Cheem TH, Liao H, Chen X, He Y. External validation of the model of thromboembolic risk in hypertrophic cardiomyopathy patients. *Can J Cardiol* 2019; **35**: 1800–1806.
72. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, Lesser JR, Udelson JE, Ackerman MJ, Maron BJ. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. *Circulation* 2008; **118**: 1541–1549.
73. Sinagra G, Elliott PM, Merlo M. Dilated cardiomyopathy: so many cardiomyopathies! *Eur Heart J* 2020; **41**: 3784–3786.
74. Koniaris LS, Goldhaber SZ. Anticoagulation in dilated cardiomyopathy. *J Am Coll Cardiol* 1998; **31**: 745–748.
75. Roberts WC, Siegal RJ, McManus BM. Idiopathic dilated cardiomyopathy: analysis of 152 necropsy patients. *Am J Cardiol* 1987; **60**: 1340–1355.
76. Bakalli A, Georgievska-Ismail L, Koçinaj D, Musliu N, Krasniqi A, Pllana E. Prevalence of left chamber cardiac thrombi in patients with dilated left ventricle at sinus rhythm: the role of transesophageal echocardiography. *J Clin Ultrasound* 2013; **41**: 38–45.
77. Natterson PD, Stevenson WG, Saxon LA, Middlekauff HR, Stevenson LW. Risk of arterial embolization in 224 patients awaiting cardiac transplantation. *Am Heart J* 1995; **129**: 564–570.
78. Mizia-Stec K, Caforio ALP, Charron P, Gimeno JR, Elliott P, Kaski JP, Maggioni AP, Tavazzi L, Rigopoulos AG, Laroche C, Frigy A, Zachara E, Pena-Pena ML, Olusegun-Joseph A, Pinto Y, Sala S, Drago F, Blagova O, Reznik E, Tendera M. Atrial fibrillation, anticoagulation management and risk of stroke in the Cardiomyopathy/Myocarditis registry of the EURObservational Research Programme of the European Society of Cardiology. *ESC Heart Fail* 2020; **7**: 3601–3609.
79. Nuzzi V, Cannatà A, Manca P, Castrichini M, Barbati G, Aleksova A, Fabris E, Zecchin M, Merlo M, Boriani G, Sinagra G. Atrial fibrillation in dilated cardiomyopathy: Outcome prediction from an observational registry. *Int J Cardiol* 2021; **323**: 140–147.
80. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. *N Engl J Med* 1994; **331**: 1564–1575.
81. Rho R, DeNofrio D, Loh E. Cardiomyopathy and embolization: risks and benefits of anticoagulation in sinus rhythm. *Curr Cardiol Rep* 2000; **2**: 106–111.
82. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, Jafri SM, Krol WF, O'Connor CM, Schulman KA, Teo K, Warren SR, WATCH Trial Investigators. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation* 2009; **119**: 1616–1624.
83. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, Di Tullio MR, Sanford AR, Mejia V, Gabriel AP, del Valle ML, Buchsbaum R, WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012; **366**: 1859–1869.
84. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. The Warfarin/Aspirin study in heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004; **148**: 157–164.
85. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK, HELAS investigators. Efficacy of antithrombotic therapy in chronic heart failure: The HELAS study. *Eur J Heart Fail* 2006; **8**: 428–432.
86. Shantsila E, Koziel M, Lip GY. Anticoagulation versus placebo for heart failure in sinus rhythm. *Cochrane Database Syst Rev* 2021; **5**: CD003336.
87. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003; **107**: 2920–2925.
88. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. *JAMA* 1994; **271**: 840–844.
89. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM, European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013; **34**: 2636–2648.
90. Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, Hare JM, Heidecker B, Heymans S, Hübner

N, Kelle S, Klingel K, Maatz H, Parwani AS, Spillmann F, Starling RC, Tsutsui H, Seferovic P, Van Linthout S. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol* 2021; **18**: 169–193.
91. Muchtar E, Blauwet LA, Gertz MA. Restrictive cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res* 2017; **121**: 819–837.
92. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, Salvi F, Ciliberti P, Pastorelli F, Biagini E, Coccolo F, Cooke RM, Bacchi-Reggiani L, Sangiorgi D, Ferlini A, Cavo M, Zamagni E, Fonte ML, Palladini G, Salinaro F, Musca F, Obici L, Branzi A, Perlini S. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation* 2009; **120**: 1203–1212.
93. Roberts WC, Waller BF. Cardiac amyloidosis causing cardiac dysfunction: analysis of 54 necropsy patients. *Am J Cardiol* 1983; **52**: 137–146.
94. Feng D, Syed IS, Martinez M, Oh JK, Jaffe AS, Grogan M, Edwards WD, Gertz MA, Klarich KW. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation* 2009; **119**: 2490–2497.
95. Donnellan E, Elshazly MB, Vakamudi S, Wazni OM, Cohen JA, Kanj M, Hanna M, Baranowski B, Saliba W, Jaber W. No association between CHADS-VASc score and left atrial appendage thrombus in patients with transthyretin amyloidosis. *JACC Clin Electrophysiol* 2019; **5**: 1473–1474.
96. Emdin M, Aimo A, Rapezzi C, Fontana M, Perfetto F, Seferovic PM, Barison A, Castiglione V, Vergaro G, Giannoni A, Passino C, Merlini G. Treatment of cardiac transthyretin amyloidosis: an update. *Eur Heart J* 2019; **40**: 3699–3706.
97. Adam RD, Coriu D, Jercan A, Bădeliţă S, Popescu BA, Damy T, Jurcuţ R. Progress and challenges in the treatment of cardiac amyloidosis: a review of the literature. *ESC Heart Fail* 2021; **8**: 2380–2396.
98. Pereira NL, Grogan M, Dec GW. Spectrum of restrictive and infiltrative cardiomyopathies: part 2 of a 2-part series. *J Am Coll Cardiol* 2018; **71**: 1149–1166.
99. Pawar A, Kumar D, Lanjewar C, Kerkar P. Steroid responsive hypereosinophilic syndrome with Loeffler's endocarditis. *Eur Heart J* 2019; **40**: 3868c.
100. Ogbogu PU, Rosing DR, Horne MK 3rd. Cardiovascular manifestations of hypereosinophilic syndromes. *Immunol Allergy Clin North Am* 2007; **27**: 457–475.
101. Calkins H, Corrado D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2017; **136**: 2068–2082.
102. James CA, Calkins H. Arrhythmogenic right ventricular cardiomyopathy: progress toward personalized management. *Annu Rev Med* 2019; **70**: 1–18.
103. Cardona-Guarache R, Åström-Aneq M, Oesterle A, Asirvatham R, Svetlichnaya J, Marcus GM, Gerstenfeld EP, Klein L, Scheinman MM. Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy: Prevalence, echocardiographic predictors, and treatment. *J Cardiovasc Electrophysiol* 2019; **30**: 1801–1810.
104. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A, Bauce B, Basso C, Brunckhorst C, Tsatsopoulou A, Tandri H, Paul M, Schmied C, Pelliccia A, Duru F, Protonotarios N, Estes NA 3rd, McKenna WJ, Thiene G, Marcus FI, Calkins H. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Eur Heart J* 2015; **36**: 3227–3237.
105. Arbustini E, Favalli V, Narula N, Serio A, Grasso M. Left Ventricular Noncompaction: A Distinct Genetic Cardiomyopathy? *J Am Coll Cardiol* 2016; **68**: 949–966.
106. Finsterer J, Stöllberger C, Towbin JA. Left ventricular noncompaction cardiomyopathy: cardiac, neuromuscular, and genetic factors. *Nat Rev Cardiol* 2017; **14**: 224–237.
107. Subahi A, Hassan AAI, Abubakar H, Ibrahim W. Isolated left ventricular non-compaction (LVNC) and recurrent strokes: to anticoagulate or not to anticoagulate, that is the question. *BMJ Case Rep* 2017; **2017**: bcr2017220954.
108. Weiford BC, Subbarao VD, Mulhern KM. Noncompaction of the ventricular myocardium. *Circulation* 2004; **109**: 2965–2971.
109. Murphy RT, Thaman R, Blanes JG, Ward D, Sevdalis E, Papra E, Kiotsekoglou A, Tome MT, Pellerin D, McKenna WJ, Elliott PM. Natural history and familial characteristics of isolated left ventricular non-compaction. *Eur Heart J* 2005; **26**:187–192.
110. Kido K, Guglin M. Anticoagulation therapy in specific cardiomyopathies: isolated left ventricular noncompaction and peripartum cardiomyopathy. *J Cardiovasc Pharmacol Ther* 2019; **24**: 31–36.
111. Stöllberger C, Finsterer J. Left ventricular hypertrabeculation/noncompaction and stroke or embolism. *Cardiology* 2005; **103**: 68–72.
112. Pignatelli RH, McMahon CJ, Dreyer WJ, Denfield SW, Price J, Belmont JW, Craigen WJ, Wu J, El Said H, Bezold LI, Clunie S, Fernbach S, Bowles NE, Towbin JA. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. *Circulation* 2003; **108**: 2672–2678.
113. Ergul Y, Nisli K, Demirel A, Varkal MA, Oner N, Dursun M, Dindar A, Aydogan U, Omeroglu RE. Left ventricular noncompaction in children and adolescents: clinical features, treatment and follow-up. *Cardiol J* 2011; **18**: 176–184.
114. Chen K, Williams S, Chan AK, Mondal TK. Thrombosis and embolism in pediatric cardiomyopathy. *Blood Coagul Fibrinol* 2013; **24**: 221–230.
115. Robinson AA, Trankle CR, Eubanks G, Schumann C, Thompson P, Wallace RL, Gottiparthi S, Ruth B, Kramer CM, Salerno M, Bilchick KC, Deen C, Kontos MC, Dent J. Off-label Use of Direct Oral Anticoagulants Compared with Warfarin for Left Ventricular Thrombi. *JAMA Cardiol* 2020; **5**: 685–692.
116. Finsterer J, Stöllberger C. Left ventricular noncompaction syndrome: genetic insights and therapeutic perspectives. *Curr Cardiol Rep* 2020; **22**: 84.
117. Sharkey SW, Lesser JR, Maron MS, Maron BJ. Why not just call it tako-tsubo cardiomyopathy: a discussion of nomenclature. *J Am Coll Cardiol* 2011; **57**: 1496–1497.
118. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International expert consensus document on Takotsubo Syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018; **39**: 2032–2046.
119. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International Expert Consensus Document on Takotsubo Syndrome (Part II): diagnostic workup, outcome, and management. *Eur Heart J* 2018; **39**: 2047–2062.
120. El-Battrawy I, Gietzen T, Lang S, Ansari U, Behnes M, Zhou X, Borggrefe M, Akin I. Short- and long-term incidence of thromboembolic events in Takotsubo Syndrome as compared with acute coronary syndrome. *Angiology* 2019; **70**: 838–843.
121. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein

J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschöpe C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KEJ, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lüscher TF. Clinical features and outcomes of Takotsubo (Stress) cardiomyopathy. *N Engl J Med* 2015; **373**: 929–938.

122. Arany Z, Elkayam U. Peripartum cardiomyopathy. *Circulation* 2016; **133**: 1397–1409.
123. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2020; **75**: 207–221.
124. Bauersachs J, Arrigo M, Hilfiker-Kleiner D, Veltmann C, Coats AJ, Crespo-Leiro MG, De Boer RA, van der Meer P, Maack C, Mouquet F, Petrie MC, Piepoli MF, Regitz-Zagrosek V, Schaufelberger M, Seferovic P, Tavazzi L, Ruschitzka F, Mebazaa A, Sliwa K. Current management of patients with severe acute peripartum cardiomyopathy: practical guidance from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2016; **18**: 1096–1105.
125. Arrigo M, Blet A, Mebazaa A. Bromocriptine for the treatment of peripartum cardiomyopathy: welcome on BOARD. *Eur Heart J* 2017; **38**: 2680–2682.
126. Cifkova R, Ferreira R, Foidart JM, Gibbs JSR, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AHEM, Morais J, Nihoyannopoulos J, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L, European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), ESC Committee for Practice Guidelines. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011; **32**: 3147–3197.
127. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, Tsikas D, Jordan J, Lichtinghagen R, von Kaisenberg CS, Struman I, Bovy N, Sliwa K, Bauersachs J, Hilfiker-Kleiner D. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. *Basic Res Cardiol* 2013; **108**: 366.
128. Bauersachs J. Poor outcomes in poor patients?: peripartum cardiomyopathy-not just black and white. *JAMA Cardiol.* 2017; **2**: 1261–1262.
129. Ntusi NB, Badri M, Gumedze F, Sliwa K, Mayosi BM. Pregnancy-associated heart failure: a comparison of clinical presentation and outcome between hypertensive heart failure of pregnancy and idiopathic peripartum cardiomyopathy. *PLoS One* 2015; **10**: e0133466.
130. Walenta K, Schwarz V, Schirmer SH, Kindermann I, Friedrich EB, Solomayer EF, Sliwa K, Labidi S, Hilfiker-Kleiner D, Bohm M. Circulating microparticles as indicators of peripartum cardiomyopathy. *Eur Heart J* 2012; **33**: 1469–1479.