A proposed strategy for anticoagulation therapy in noncompaction cardiomyopathy

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Abstract

Noncompaction cardiomyopathy (NCCM) is a rare condition characterized by prominent trabeculae, deep intertrabecular recesses, and a left ventricular myocardium with a two-layered structure, characterized by a spongy endocardial layer and a thinner and compacted epicardial one. NCCM can be isolated or associated with other congenital heart diseases and complex syndromes involving neuromuscular disorders and facial dysmorphisms. To date, more than 40 genes coding for sarcomeric, cytoskeletal, ion channels, and desmosomal proteins have been identified. Clinical presentation is also highly variable, ranging from no symptoms to end-stage heart failure (HF), lethal arrhythmias, sudden cardiac death, or thromboembolic events. In particular, the prevalence of thromboembolism in NCCM patients appears to be higher than that of a similar, age-matched population without NCCM. Thromboembolism has a multifactorial aetiology, which is linked to genetic, as well as traditional cardiovascular risk factors. In previous studies, atrial fibrillation (AF) was observed in approximately 25–30% of adult NCCM patients and embolism had a cardiac source in ~63–69% of cases; therefore, AF represents a strong predictor of adverse events, especially if associated to HF and neuromuscular disorders. Left ventricular dysfunction is another risk factor for thromboembolism, as a result of blood stagnation and local myocardial injury. Moreover, it is not completely clarified if the presence of deep intertrabecular recesses causing stagnant blood flow can constitute per se a thrombogenic substrate even in absence of ventricular dysfunction. For the clinical management of NCCM patients, an appropriate stratification of the thromboembolic risk is of utmost importance for a timely initiation of anticoagulant therapy. The aim of the present study is to review the available literature on NCCM with particular attention on thromboembolic risk stratification and prevention and the current evidence for oral anticoagulation therapy. The use of direct oral anticoagulants vs. vitamin K antagonists is also discussed with important implications for patient treatment and prognosis.

Keywords Noncompaction cardiomyopathy; Atrial fibrillation; Anticoagulant therapy; Left ventricular dysfunction; Thrombosis; Stroke

Received: 14 June 2021; Revised: 19 September 2021; Accepted: 25 October 2021
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Introduction

Noncompaction cardiomyopathy (NCCM) is a rare condition characterized by prominent left ventricular (LV) trabeculae and deep intertrabecular recesses, first described in 1969 by Feldt et al., who reported a biventricular spongy myocardium in a female patient who died at the age of 3 months. NCCM is characterized by a two-layered myocardial structure, characterized by a spongy endocardial layer and a thinner and compacted epicardial one. Apical and lateral segments of the LV are the most commonly involved, but both ventricles can be affected.

The prevalence of NCCM is unknown, but it has been estimated to be approximately 0.05–0.27% among adults...
referred to echocardiography lab,² with males more affected than females.³ Age at the time of diagnosis is variable from early infancy to late adulthood.³

Noncompaction cardiomyopathy is a genetic cardiomyopathy, because it has been described in association with mutations in more than 40 genes coding for sarcomeric, cytoskeletal, Z-line, and mitochondrial proteins⁴ and even in chromosomal defects.³ A strong genotype–phenotype correlation has been reported for Hyperpolarization Activated Cyclic Nucleotide gated potassium channel 4 (HCN4), Titin (TTN), and Lamin A/C (LMNA) mutations, with a high incidence of heart failure (HF) and ventricular arrhythmias.⁵ Furthermore, NCCM can be associated to genetic syndromes, including congenital heart disease, neuromuscular disorders, and facial dysmorphisms.⁵

From a pathogenetic point of view, NCCM may be due to an abnormal myocardial compaction during intrauterine cardiac development.⁶ However, some authors have suggested that NCCM could be the result of abnormal persistence of the trabecular layer rather than the effect of noncompaction of the ventricular wall.⁶

Clinical presentation of NCCM is highly variable, ranging from no symptoms to end-stage HF, lethal arrhythmias, sudden cardiac death, or thromboembolic events (stroke, transient ischaemic attack, mesenteric, myocardial and renal infarction, or peripheral embolism).³,⁷,⁸

As far as the diagnosis is concerned, transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (MRI) are the most common imaging techniques (Figure 1), but recent studies showed the ability of low-dose cardiac computer tomography in identifying ventricular trabeculation⁹–¹¹; ventricular angiography can be advised in selected cases with uncertain diagnosis or in patients who need an invasive cardiac study¹² (Figure 1).

Several diagnostic criteria have been proposed, but there is currently no gold standard. The most used criteria are the Jenni criteria¹³ for TTE and the Petersen criteria¹⁴ and Jacquier criteria¹⁵ for cardiac MRI (Table 1). Endomyocardial biopsy should be considered if myocarditis is suspected or if new onset acute HF occurs in a previously haemodynamically stable NCCM patient.¹⁰

As a result of the very low prevalence of the disease, there is a lack of evidence from large randomized trials about the clinical management of NCCM, especially regarding the need for anticoagulation. Therefore, it may be challenging to identify the optimal candidates for and when to start anticoagulant therapy, particularly if LV size and function are normal or in case of systolic dysfunction and sinus rhythm. Thus, we searched the Medline, Embase, and Google Scholar databases from inception to April 2021, and we found 174 articles describing the thromboembolic risk and the anticoagulation strategy adopted in NCCM patients; the full search strategies are provided in the supporting information. The aim of this review is to stratify the thromboembolic risk in NCCM patients and shed light on the potential indications for anticoagulant therapy.

**Thromboembolic risk in noncompaction cardiomyopathy**

The frequency of thromboembolism in NCCM patients is quite variable (0–38%) and seems to be age related: overall, adults have an increased risk of experiencing an embolic event than children (Table 2).³ As an example, although Chin et al. described three children out of eight (38%) with clinically evident systemic embolism,¹⁶ in subsequent studies, no thromboembolic events occurred during the entire
follow-up period. On the contrary, in a large retrospective study of 169 NCCM adult patients, 15% experienced thromboembolic events: 92% of them had a stroke and 8% had a peripheral embolism. The cause of thromboembolism was cardioembolic (69%), atherosclerotic (19%), and undetermined (12%); among the 18 patients with cardioembolic stroke, only 7 (39%) had atrial fibrillation (AF) while 14 (78%) had LV systolic dysfunction. In the cardioembolic

Table 1 Diagnostic criteria used to define noncompaction cardiomyopathy

| Echocardiographic criteria | MRI criteria |
|---------------------------|-------------|
| **Jenni et al.**<sup>13</sup> | A two-layer structure with a thin, compacted layer (C) and a thickened non-compacted layer (NC) at end-systole | A ratio of NC/C > 2 measured at end-diastole |
| **Chin et al.**<sup>16</sup> | Distance from the epicardial surface to the trough of the trabecular recess (X) and distance from the epicardial surface to peak of trabeculation (Y) at end-diastole ≥ 3 trabeculations along the LV endocardial borders, different from the papillary muscles, false tendons, and aberrant muscle bands | A ratio of X/Y ≤ 0.5 |
| **Stöllberger et al.**<sup>17</sup> | Identification of the bilayered myocardium in the short-axis views at the middle and apical levels | Trabeculations with the same echogenicity as the myocardium and synchronous movement with ventricular contractions |
| **Paterick et al.**<sup>18</sup> | | A ratio of NC/C ≥ 2, measured at end-diastole on short-axis parasternal views |

| C, compacted; LV, left ventricular; MRI, magnetic resonance imaging; NC, non-compacted. |

Table 2 Thromboembolic events in noncompaction cardiomyopathy patients

| Study | No. of patients | Incidence of thromboembolic events | Type of thromboembolic event |
|-------|----------------|----------------------------------|-----------------------------|
| Ritter et al.<sup>21</sup> | 17 | 29% | 3 TIA |
| Oechslin et al.<sup>22</sup> | 34 | 24% | 1 Stroke |
| **Aras et al.**<sup>23</sup> | 67 | 9% | 1 PE |
| Murphy et al.<sup>24</sup> | 45 | 4% | 6 TIA |
| Stöllberger and Finsterer<sup>25</sup> | 62 | 10% | 2 Stroke |
| Stöllberger et al.<sup>26</sup> | 169 | 15% | 1 TIA |
| Greutmann et al.<sup>27</sup> | 115 | 4% | 5 Stroke/TIA |
| Stöllberger et al.<sup>28</sup> | 144 | 15% | 1 PE |

| Paediatric population | |
|-----------------------|----------------|
| Ichida et al.<sup>29</sup> | 27 | 0 | 2 Stroke |
| Chin et al.<sup>16</sup> | 8 | 38% | 1 Abdominal embolization |
| Pignatelli et al.<sup>30</sup> | 36 | 0 | |
| Wald et al.<sup>31</sup> | 22 | 0 | |

PE, pulmonary embolism; TIA, transient ischaemic stroke.
group, 50% of patients was receiving acetylsalicylic acid (ASA) 100 mg/day, 6% was receiving vitamin K antagonists (VKAs), 6% was receiving low-molecular weight heparin, and 38% was not taking any antithrombotic or anticoagulant therapy. Another study by the same authors reported similar findings: thromboembolic events occurred in 22 (15.3%) of 144 NCCM patients (21 ischaemic strokes and 1 peripheral embolism). At the time of thromboembolism, 59% of patients was receiving ASA 100 mg/day, 4.5% VKA with an international normalized ratio (INR) below the therapeutic range, 4.5% low-molecular weight heparin, and 32% was not taking antithrombotic or anticoagulant therapy.

These findings suggest that the treatment with ASA, administered in ~60% of NCCM patients, was not able to prevent the occurrence of thromboembolic events. As a matter of fact, thromboembolism in NCCM patients has a multifactorial aetiology, including genetic and other well-known cardiovascular risk factors.5

A recent study by van Waning et al.33 correlated genetics, phenotype, and outcomes; myosin heavy chain 7 (MYH7), myosin binding protein C3 (MYBPC3), and TTN mutations were the most common (71%) and were frequently associated with LV dysfunction. Furthermore, children with MYBPC3 complex mutations had a higher risk of major adverse cardiovascular events, including cardioembolic stroke, than patients with MYH7 mutations.33

Genotype variability is associated with an equally varied phenotype presentation; one of the intriguing findings among patients with isolated LV noncompaction is the presence of associated neuromuscular disorders, reported in more than four-fifths of subjects.34 Patients with NCCM and neuromuscular disorders appear to have a higher thromboembolic risk and a worse prognosis, probably related to the earlier onset of severe LV dysfunction, the frequent involvement of respiratory muscles resulting from the underlying neuromuscular disorders, and the precluded decision for heart transplantation.35 Moreover, NCCM is also associated with congenital heart diseases; cardiac abnormalities, in particular atrial (3.5%) and ventricular defects (2.5%), have been described in 12% of patients.36 In this setting, thrombi could originate from the right ventricle or right atrium and reach the systemic circulation through a ventricular or atrial septal defect.

More challenging is the assessment of thromboembolic risk in NCCM patients without AF, LV dysfunction, and/or LV thrombus; specifically it is still controversial whether NCCM alone is an independent risk factor for stroke. Given the complexity of the cardiomyopathy, CHADS2 score, developed for AF patients, could be used for thromboembolic risk stratification. Stöllberger et al.26 evaluated the prognostic value of CHADS2 and CHA2DS2-VASc scores in NCCM patients with and without previous thromboembolic events. They observed that patients with NCCM and a history of thromboembolic events have a significantly higher CHADS2/CHA2DS2-VASc score. Of note, CHADS2 was superior to CHA2DS2-VASc in predicting the thromboembolic risk; this may be explained by the younger age of NCCM patients and the male preponderance. Therefore, in NCCM patients without a clear indication to anticoagulant therapy (AF, previous thromboembolism, or intracardiac thrombi), CHADS2 score may be more accurate than CHA2DS2-VASc for thromboembolic risk stratification and, if the CHADS2 is ≥2, oral anticoagulation should be strongly considered.

Noncompaction cardiomyopathy and atrial fibrillation

Atrial fibrillation is the common atrial arrhythmia affecting ~25–30% of patients with NCCM.37 In a previous study on 68 adult NCCM patients followed up for approximately 61 months, AF occurred in 29.4%.38 A similar incidence of AF has been reported in children with NCCM. These findings suggest that this cardiomyopathy may act as a proarrhythmic substrate for either the atria or the ventricles.30

Noncompaction cardiomyopathy patients developing AF tend to have a higher prevalence of valvular abnormalities, a more extensive noncompaction layer, and a worst LV systolic function than NCCM patients without AF.37,38 These findings could partially explain the pathophysiology of AF; in adult patients, atrial cardiopathy may be correlated to atrial dilatation due to systolic dysfunction and ativoventricular valve regurgitation or to the underlying cardiomyopathy and ion channel imbalances.39

In NCCM patients, embolism have a cardiac source in ~63–69% of cases26,28 and AF represents a strong predictor for mortality, especially if associated to HF and neuromuscular disorders.29,37 Therefore, an appropriate anticoagulation therapy for NCCM patients with AF or previous embolic event is mandatory.40 In particular, there is much stronger evidence that oral anticoagulation is associated with a higher reduction in stroke rate compared with antiplatelet agents (60% vs. 20%, respectively).41

Noncompaction cardiomyopathy and left ventricular dysfunction with and without thrombosis

Noncompaction cardiomyopathy patients with LV dysfunction (ejection fraction < 50%) and sinus rhythm should be considered as high-risk patients for thromboembolic events.42 Indeed, in this group, LV dysfunction plays a crucial role in the predisposition to thrombus formation due to blood stagnation and local myocardial injury within the deep intertrabecular recesses.

In a nested case–control study of patients with severe LV dysfunction without AF, the stroke incidence was 3.9% over 35 months, with a significantly higher incidence in patients affected by NCCM (P = 0.02), LV aneurysm (P < 0.01), and
pulmonary hypertension ($P < 0.001$). Therefore, in NCCM patients with LV systolic dysfunction and sinus rhythm, long-term oral anticoagulation is generally suggested.

Left ventricular thrombosis in NCCM patients with LV dysfunction may be a terrible complication because it is associated with high rates of systemic embolism, morbidity, and mortality. Compared with echocardiography, cardiac MRI offers a higher resolution for the identification of myocardial trabeculations and provides a more accurate tissue characterization, allowing for the correct identification of apical thrombi and endomyocardial fibrosis. Therefore, cardiac MRI should be the first choice in all NCCM patients as it can provide valuable information for a better thromboembolic risk stratification. If an LV thrombus is identified, VKA is considered the standard of care; nevertheless, there is increasing evidence that direct oral anticoagulants (DOACs) are associated with a high rate of complete resolution of intracardiac thrombosis with a low rate of thromboembolic or haemorrhagic complication.

Noncompaction cardiomyopathy per se

In a large retrospective study has been reported a thromboembolic event of unknown origin in NCCM patients with CHA$_2$DS$_2$VASc score = 0, suggesting that NCCM may have per se an intrinsic thromboembolic risk. It has also been reported that NCCM patients with preserved ejection fraction and positive late gadolinium enhancement (LGE) at cardiac MRI have an increased risk of cardiovascular events, including stroke, than NCCM patients with preserved systolic function without LGE.

Autopsy and endomyocardial biopsy studies in patients with NCCM showed the presence of viable cells separated by large, deep, unendothelialized endomyocardial channels. Deep intertrabecular recesses cause stagnant blood flow, which can result in thrombus formation even in absence of ventricular dysfunction. Possible pathogenesis of thrombus formation is showed in Figure 3.

All the Virchow’s triad factors—sluggish blood flow in deep intertrabecular recesses, local myocardial injury, and hypercoagulability/stasis of flow—which contribute to formation of LV thrombus, are present in NCCM, which can also be associated with a hypercoagulability state due to overexpression of factor VIII and endothelin-1.

In the current literature, two large studies have highlighted a direct association between NCCM and juvenile ‘cryptogenic’ stroke: 12–14% patients with NCCM and no other concomitant comorbidities or risk factors (i.e. PFO) experienced an undetermined thromboembolic event, confirming that NCCM may carry a cardioembolic risk per se.
A recent case–control study in young adults (age 18–49) presenting with an imaging-positive ischaemic stroke of undetermined aetiology showed that the percentage of non-compacted LV volume was higher in patients with cryptogenic stroke compared with stroke-free controls of similar age and gender. Importantly, a 5% increase in non-compacted ventricular volume at cardiac MRI has been associated with a nine-fold increased risk of cryptogenic ischaemic stroke. Furthermore, several case reports seem to confirm the close relationship between NCCM and juvenile stroke.

**Stroke prevention in noncompaction cardiomyopathy**

In the ‘2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy’, anticoagulation therapy is recommended in NCCM patients with AF and in those with previous thromboembolic events or LV thrombosis (Class I, Level of Evidence B) while may be reasonable in individuals with NCCM with LV dysfunction (Class IIb, Level of Evidence B). In AF patients, the landscape of oral anticoagulant therapy has widely changed in the last decade. Randomized control trials have demonstrated the effectiveness and safety of DOACs. Subsequent data from registries and real-world experiences have established DOACs as a valid alternative to warfarin. Given the remarkable safety profile of DOACs compared with VKAs, emerging evidence supports their use in high-risk populations such as elderly, renal impairment, peripheral artery disease, and AF in the context of congenital heart disease and cardiomyopathies. Similarly, several case reports have demonstrated that DOACs could be at least as effective and safe as warfarin in preventing cardioembolic events in NCCM patients. Skidan et al. reported a case of a 32-year-old male with NCCM and isolated LV apical hypoplasia admitted to the hospital for radiofrequency catheter ablation of persistent AF. Despite the high thromboembolic risk due to the concomitant presence of AF and biventricular systolic dysfunction, no thromboembolic events occurred during 2 years of follow-up in NCCM patients receiving long-term oral anticoagulation therapy with Rivaroxaban. Similarly, Li et al. described the history of a 54-year-old man with hypertension, diabetes, and end-stage renal disease presented with 1 day palpitations and lightheadedness following a dialysis session. Electrocardiogram revealed AF with normal ventricular rate while TTE revealed prominent trabeculation and normal LV systolic function, suggestive of NCCM. Although heparin was firstly administered, the patient was switched to Apixaban for outpatient treatment; during follow-up, no thromboembolic events were reported.

Regarding the presence of LV thrombosis, long-term VKA administration is still the most commonly adopted therapeutic strategy. In a multicentre study enrolling patients with LV thrombi, DOAC treatment was associated with a higher risk of thromboembolic events compared with warfarin. Although these findings seem to corroborate the assumption that the ideal anticoagulant treatment for LV thrombus is warfarin, the authors reported several study limitations: for example,
bleeding events were not considered as an endpoint and no information on DOAC dosing was provided. Thus, no conclusive data are available on the use of DOACs in patients with NCCM and LV thrombus, and further studies with comparative groups are necessary.

As a matter of fact, several recent studies have shown that DOACs represent a new promising strategy for treating LV thrombus. Fledderman et al. demonstrated that in 83% of patients, DOACs safely and effectively led to complete resolution of LV thrombus. Additionally, a meta-analysis of 33 papers showed thrombus resolution in 80% of patients treated with DOACs. Undoubtedly, only prospective randomized clinical trials may determine the most effective treatment strategies for LV thrombi.

In the specific setting of LV thrombosis in NCCM patients, a single case report about treatment with DOACs is currently available: in a 43-year-old patient, treatment with Rivaroxaban at low dose (10 mg once daily) resulted in thrombus resolution at 3 months of follow-up. Probably, DOACs may offer in the next future a new alternative therapeutic approach in NCCM patients with LV thrombosis and/or systolic dysfunction. Well-known therapeutic advantages of DOACs, including improved safety, reduced risk of bleeding, increased adherence to therapy, and convenience during long life oral therapy, could be precisely useful in young NCCM patients, especially in children. The latter category is the most challenging one because no randomized trials on DOACs have been published for paediatric patients and VKAs still represent the first-choice anticoagulation therapy. Unfortunately, VKAs have numerous drug interactions, as well as their efficacy can be influenced by the vitamin K intake from the diet. This factor is a major limitation especially in children who rapidly change their diet altering their vitamin K consumption. Therefore, monitoring oral anticoagulant therapy in children is difficult and requires close supervision, with frequent dose adjustments. During initiation of therapy, monitoring should be daily or every few days, and when INR is high, lifestyle changes are necessary and physical activity may be forbidden. Moreover, because of the increased bleeding risk associated with oral anticoagulation, children are often hovered over by their parents and may have psychological problems, such as depression and anxiety. In this setting, the use of DOACs could potentially overcome several difficulties (i.e. need for INR evaluation and diet control), but further study is necessary.

Another debated issue is the need for oral anticoagulant therapy in NCCM patients with LV dysfunction alone. Although in general population the thromboembolic risk is directly proportional to the severity of LV dysfunction, current evidence does not recommend long-term anticoagulation therapy. In spite of this, NCCM patients with LV dysfunction and sinus rhythm should be considered at high risk for thromboembolic events. As previously described, the presence of NCCM in patients with severe systolic dysfunction was associated with higher risk of thromboembolism. Moreover, in a recent meta-analysis,
NCCM patients with LV dysfunction and LGE at cardiac MRI were compared with those without LGE; patients with LGE experienced more frequently cardiovascular adverse events, including stroke.46 Thus, in NCCM patients with LV dysfunction (ejection fraction < 50% as defined in the 2016 Guidelines for the diagnosis and treatment of acute and chronic heart failure), long-term anticoagulation is suggested and the use of DOACs should be preferred.42 Regarding patients with NCCM without AF, systolic dysfunction, and/or ventricular thrombosis, current evidence suggests that NCCM is a thromboembolic substrate per se because young patients with no other cardiovascular risk factors have experienced a ‘cryptogenic’ stroke.52 Therefore, although the prevention therapy of thromboembolic events in these patients has not been recommended yet, the use of anticoagulant therapy may be considered in patients with CHADS2 score ≥ 2.

A flow chart to summarize the current and potential indications of anticoagulation therapy in NCCM patients is shown in Figure 4; anticoagulation is mandatory in all NCCM patients with AF, previous thromboembolic events, or LV thrombosis, whereas it should be considered in NCCM patients with LV dysfunction and sinus rhythm.40 In patients with normal LV size and function, better stratification of thromboembolic risk by evaluating CHADS2 score is suggested. In our opinion, the use of DOACs should be taken into consideration in all NCCM patients in absence of contraindication and following a careful evaluation of each single case, mainly because of the long-life expectancy of affected patients, the reduced risk of bleeding, and the larger adherence and persistence to therapy.

Conclusions
Noncompaction cardiomyopathy is a complex, clinically and genetically heterogeneous disorder characterized by an increased thromboembolic risk. Long-term oral anticoagulant therapy is recommended in NCCM patients with AF and previous thromboembolic events while it seems reasonable in those with LV dysfunction. Based on latest findings and our clinical experience, DOACs may be used as first choice. Although a better clinical stratification and pathophysiologic understanding are necessary, NCCM per se might represent an embolic risk factor that requires anticoagulant therapy for stroke prevention.

Conflict of interest
Nothing to disclose.

Supporting information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Study Strategy.

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