

## Presentation, management and outcomes of thrombosis for children with cardiomyopathy

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**BACKGROUND:** Thrombosis in children with dilated and inflammatory cardiomyopathy is an unpredictable complication with potentially important morbidity.

**OBJECTIVE:** To determine the prevalence, associated factors, management and outcomes of thrombosis in this setting.

**METHODS:** Data were obtained from review of medical records. Factors associated with thrombosis and the impact on outcome were sought.

**RESULTS:** From 1990 to 1998, 66 patients that presented with dilated cardiomyopathy were followed for a median interval of 1.4 years (range 0 to 9.79 years) from first presentation. Thrombosis was diagnosed in four patients at presentation and in four patients during follow-up. Thrombosis was noted in one additional patient at examination after death. The overall nine-year period prevalence of thrombosis was 14%. Anticoagulation was started at presentation in 31% of patients. The mean left ventricular ejection fraction at presentation was significantly lower in those given anticoagulation ( $19 \pm 8\%$ ) versus those who were not ( $32 \pm 15\%$ ;  $P < 0.001$ ). The mean ejection fraction at presentation was similar in those patients with ( $25 \pm 10\%$ ) versus those without thrombosis ( $28 \pm 15\%$ ;  $P = 0.44$ ). During follow-up, 11 patients died and seven underwent cardiac transplantation. Kaplan-Meier estimates of freedom from death or transplantation were 88% at three months, 81% at one year and 70% at five years. Survival free of transplantation was not affected by thrombosis.

**CONCLUSIONS:** Thrombosis is common in children with cardiomyopathy, can occur at any time in the patients' clinical course and is not related to clinical features or survival free of transplantation. The relevance and prevention of thrombosis in this setting remains unclear.

**Key Words:** *Anticoagulants; Cardiomyopathy; Coagulation; Thrombosis; Thrombus*

There are numerous reports addressing the natural history and outcomes of children with dilated cardiomyopathy (DCM) and inflammatory cardiomyopathy (1-6). However, the prevalence of cardiac thrombosis has not been well defined (7-9). Multiple factors have been implicated in causation, including impaired left ventricular (LV) systolic function, stasis of blood flow, the presence of an abnormal endocardial surface, dysrhythmias and a hypercoagulable state (10-15). The interplay

## La présentation, la prise en charge et les issues de la thrombose chez les enfants atteints de myocardiopathie

**HISTORIQUE :** La thrombose chez les enfants atteints d'une myocardiopathie dilatée et inflammatoire est une complication imprévisible dont la morbidité peut être marquée.

**OBJECTIF :** Déterminer la prévalence, les facteurs connexes, la prise en charge et les issues de la thrombose dans ce contexte.

**MÉTHODOLOGIE :** Les données ont été obtenues grâce à l'examen de dossiers médicaux. Les facteurs associés à la thrombose et les répercussions sur les issues ont été évalués.

**RÉSULTATS :** De 1990 à 1998, 66 patients qui avaient consulté en raison d'une myocardiopathie dilatée ont été suivis pendant un intervalle médian de 1,4 an (plage de 0 à 9,79 ans) après la première consultation. Une thrombose a été diagnostiquée chez quatre patients à la présentation et chez quatre patients pendant le suivi. On l'a aussi constatée chez un patient supplémentaire à l'examen après le décès. La prévalence globale de thrombose pendant la période de neuf ans s'élevait à 31 % des patients. La fraction d'éjection ventriculaire gauche moyenne à la présentation était considérablement plus faible chez les patients qui avaient reçu des anticoagulants ( $19 \pm 8\%$ ) que chez ceux qui n'en avaient pas reçu ( $32 \pm 15\%$ ;  $P < 0,001$ ). La fraction d'éjection moyenne à la présentation était similaire chez les patients atteints de thrombose ( $25 \pm 10\%$ ) et chez les patients sans thrombose ( $28 \pm 15\%$ ;  $P = 0,44$ ). Pendant le suivi, 11 patients sont décédés, et sept ont subi une greffe cardiaque. Les évaluations de Kaplan-Meier sur l'absence de décès ou de greffe étaient de 88 % au bout de trois mois, de 81 % au bout d'un an et de 70 % au bout de cinq ans. La thrombose n'avait pas d'effet sur la survie sans greffe.

**CONCLUSIONS :** La thrombose est courante chez les enfants atteints d'une myocardiopathie, peut se manifester en tout temps pendant l'évolution clinique et n'est pas reliée aux caractéristiques cliniques ou à la survie sans greffe. Dans ce contexte, la pertinence et la prévention de la thrombose demeurent nébuleuses.

between these factors is not fully defined. Systemic anticoagulation is often initiated empirically, based on the degree of LV dysfunction and dilation or the detection of intracardiac thrombosis in the absence of clinical signs of embolism. Given the lack of knowledge regarding the risk of thrombosis and its prevention and management in this setting, we sought to determine the prevalence, associated factors, management and outcomes of cardiac thrombosis in children with DCM.

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**TABLE 1**  
**Clinical features at presentation (n=66)**

Main symptoms or signs, %	
Congestive heart failure	60
Shock	5
Dyspnea	8
Poor eating habits	1
Endocardial fibroelastosis on echocardiography, %	13
Additional diagnoses, %	
Genetic abnormality	22
Metabolic abnormality	7
Previous myocarditis	13
Presence of noncardiac problem	19
Family history of cardiomyopathy	18

## METHODS

### Study population

All patients presenting to The Hospital for Sick Children, Toronto, Ontario, from 1990 to 1998 with DCM but without underlying structural heart disease were included in the present study.

### Measurements

Data regarding patient demographics, diagnostic tests, and management at presentation and during follow-up were obtained from the hospital's cardiomyopathy database and medical records. Evidence of the presence of a thrombus at presentation or during follow-up was sought by review of diagnostic reports (echocardiograms and angiograms), pathology reports on explanted hearts and autopsy reports. In the event of occurrence of a thrombus, data regarding subsequent management and clinical outcomes were obtained.

### Data analysis

Data are described as frequencies, medians with ranges, and means with SDs as appropriate. Kaplan-Meier estimates were used to plot survival. Log rank tests were used to compare survival for patients with versus those without thrombosis. Factors associated with the presence of thrombus were sought using Fisher's exact tests,  $\chi^2$  tests, Student's *t* tests and Kruskal-Wallis ANOVAs as appropriate. All statistical analyses were performed using SAS statistical software version 9 (SAS Institute Inc, USA) using default settings.

## RESULTS

### Patient characteristics

Between 1990 and 1998, 66 patients (59% male) presented with DCM at a median age of 2.3 years (range birth to 17.8 years). Clinical features at presentation are shown in Table 1.

### Frequency of thrombosis

A cardiac thrombus was noted at presentation by echocardiography in four patients and in a further four patients during subsequent follow-up. The median interval of follow-up was 1.4 years (range 0 to 9.8 years) from first presentation. It was reported at autopsy in only one additional patient. None of these patients had any known prothrombotic disorders or cardiac arrhythmias. There was no report of a thrombus in the seven explanted hearts of the patients who had undergone cardiac transplantation. The overall nine-year period prevalence of thrombosis was 14%.

**TABLE 2**  
**Characteristics of the patients who had thrombosis at presentation (n=4)**

Characteristics	Patient			
	1*	2	3†	4
Age at presentation	15 days	4.8 years	8.4 years	14.3 years
Initial EF, %	42	23	22	23
Initial shortening fraction, %	19	N/A	10	14
LV thrombus	No	Yes	Yes	Yes
RV thrombus	Yes	No	No	No
LVED, cm	1.40	5.10	4.79	7.1
RVED, cm	0.80	2.20	1.95	1.21
Mitral regurgitation	Trivial	Mild	Moderate	Mild
Tricuspid regurgitation	Mild	Moderate	Mild	Mild
Intravenous inotropes used	No	Yes	Yes	No
Embolism (CNS)	No	No	No	Yes
Length of hospital stay, days	10	17	7	26
Further intracardiac thrombosis	No	Yes‡	No	No
Heart transplantation	No	No	Yes	Yes
Died	No	Yes	No	No

\*Possible defect in fatty acid oxidation; †Mitochondrial myopathy; ‡Left ventricular (LV) thrombus found by echocardiography at three-month (ejection fraction [EF] 26%) and four-year (EF 19%) follow-up appointments. CNS Central nervous system; LVED Left ventricle end-diastolic dimension; N/A Not available; RV Right ventricular; RVED Right ventricle end-diastolic dimension

### Thrombosis at clinical presentation

The characteristics of the four patients with cardiac thrombosis at presentation are shown in Table 2. The thrombus was located by echocardiography in the right ventricular (RV) apex in patient 1, and in the LV apex in patients 2, 3 and 4. Patient 2 had an additional thrombus adherent to the anterior LV wall at presentation, and two additional LV apical thrombi were found by echocardiography at the three-month and four-year follow-up appointments. Patient 4 also had an additional thrombus adherent to the anterior leaflet of the mitral valve at presentation.

Patient 1 presented to the hospital in cardiac failure and was later diagnosed with a possible metabolic defect in fatty acid oxidation. Patients 2 and 3 presented with fatigue and were referred to the cardiology service to rule out myocarditis. Cardiac biopsy results for both patients were negative for myocarditis. Patient 3 was later found to have a mitochondrial myopathy. Patient 4 was brought to the hospital with symptoms of slurred speech and ataxia following a thromboembolic stroke. Cardiac transplantations were performed for patients 3 and 4. The donor hearts were subsequently well tolerated with minimal rejection episodes and excellent ventricular function for both patients. The diagnosis of DCM was made for all patients following their initial echocardiograms. Only one of the four patients died following DCM diagnosis. The three other patients were discharged home in stable condition.

### Factors associated with thrombosis at presentation

There were no significant differences noted with regard to patient demographics, echocardiographic variables or anticoagulation use between patients with versus without thrombosis at presentation.

### Presentation of cardiac thrombosis during follow-up

The characteristics of the four patients who developed thrombosis during follow-up are presented in Table 3. Thrombus was

**TABLE 3**  
**Characteristics of the patients who developed thrombosis during follow-up (n=4)**

Characteristics	Patient			
	5	6	7	8
Age at presentation	2.9 months	1.0 years	2.3 years	3.4 years
Interval to thrombus	19 days	15 days	20 days	2.8 months
Initial EF, %	23	33	39	15
EF at time of thrombosis, %	31	11	19	20
Initial shortening fraction, %	N/A	16	18	12
LV thrombus	No	Yes	Yes	Yes
RV thrombus	Yes	No	No	No
LVED, cm	3.35	4.96	5.16	4.30
RVED, cm	2.77	1.19	1.14	N/A
Mitral regurgitation	Severe	N/A	Mild	Moderate
Tricuspid regurgitation	Mild	Mild	N/A	Moderate
Embolism	No	No	No	No
Length of hospital stay, days	19	15	36	90
Further intracardiac thrombosis	No	No	No	Yes*
Heart transplantation	No	No	No	Yes
Died	No	No	No	Yes

\*Left ventricular (LV) thrombus found by echocardiography at 4.5-year follow-up appointment with ejection fraction (EF) of 5%. LVED Left ventricle end-diastolic dimension; N/A Not available; RV Right ventricular; RVED Right ventricle end-diastolic dimension

noted in the RV for patient 5 at cardiac catheterization and biopsy. The thrombus was identified on echocardiography in the LV for patients 6, 7 and 8, who all survived to hospital discharge. Within the LV, the location was in the ventricular apex for patients 6 and 7. An LV mural thrombus was found in patient 8. Patient 8 also had additional cardiac thrombi in both LV and RV apices, located by echocardiography 4.5 years after DCM diagnosis. This patient subsequently died due to hyperacute rejection after cardiac transplantation. All four patients had very low initial ejection fraction (EF) and had received intravenous inotropic agents. Thrombosis was noted at varying intervals after presentation.

LV thrombus was found in patient 9 at autopsy only. This patient died due to cardiac collapse secondary to inflammatory cardiomyopathy and had not been known to have thrombosis during life.

#### Anticoagulation therapy

Of the 66 patients with DCM, 21 (32%) were started on anticoagulation at presentation, including those with thrombosis. Warfarin was used in 18 patients, heparin in two patients and warfarin with acetylsalicylic acid in one patient. Patients who received anticoagulation had significantly lower mean ( $\pm$  SD) initial EF ( $19\pm 8\%$  versus  $32\pm 15\%$ , respectively;  $P<0.001$ ) and higher mean LV end-diastolic dimensions ( $5.33\pm 1.58$  cm versus  $4.18\pm 1.52$  cm, respectively;  $P<0.001$ ). This difference persisted after adjusting in a linear regression model for the difference in age at presentation (5.4 versus 1.4 years, respectively;  $P=0.12$ ) of patients who received versus those who did not receive anticoagulation.

The data for anticoagulation therapy for patients with thrombosis are presented in Table 4. No patients were on anticoagulation therapy before DCM diagnosis. Seven of the nine patients with thrombosis were started on anticoagulation after the discovery of their thrombus. These patients were first started

**TABLE 4**  
**Anticoagulation therapy**

	Patient								
	1	2	3	4	5	6	7	8	9
Anticoagulation therapy before thrombosis	No	No	No	No	No	Yes	Yes	Yes	No
INR/PT in therapeutic range at the time of thrombosis	No	No	No	No	No	No	Yes	U*	No
Anticoagulation therapy after thrombosis	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Further thrombosis	No	Yes	No	No	No	No	No	Yes	NA†

\*International normalized ratio (INR) between 1.5 and 2.5 during hospital stay; †Thrombus found in autopsy. NA Not applicable; PT Prothrombin time; U Unknown

with intravenous heparin, followed by oral warfarin, with the goal of maintaining an international normalized ratio (INR) between 2.5 and 3.5. However, only one patient was able to maintain an INR in the therapeutic range during their hospital stay. An additional patient was able to achieve an INR between 1.5 and 2.5. Two of the eight patients receiving oral anticoagulants had incidents of further thromboembolic events. Three of the four patients who had thrombosis during follow-up were on anticoagulation therapy before the discovery of their cardiac thrombus. Patients 5 and 9 were never placed on anticoagulation therapy. No patients received thrombolytic agents.

#### Survival and cardiac transplantation

There were three total deaths among those with thrombosis. Of the eight patients who presented with thrombi at either presentation or follow-up, the only two deaths included both patients who presented with multiple thrombotic events (patients 2 and 8). Cardiac transplantation was performed in seven patients. Kaplan-Meier estimates of freedom (95% CI) from death or transplantation were 88% (82% to 92%) at three months, 81% (74% to 87%) at one year and 70% (60% to 80%) at five years.

#### Factors associated with thrombus formation

Mean EF values for patients with and without thrombosis are shown in Figure 1. The mean initial EF was similar in those without versus those with thrombosis ( $29\pm 15\%$  versus  $24\pm 9\%$ , respectively;  $P=0.42$ ). However, the mean EF at the time of thrombosis was significantly different than the mean initial EF of those without thrombosis ( $21\pm 9\%$  versus  $29\pm 15\%$ , respectively;  $P<0.05$ ). There was a decrease in the mean EF for those patients who developed thrombosis at follow-up ( $25\pm 7.5\%$  at initial presentation versus  $17\pm 5.3\%$  at follow-up at the time of thrombosis;  $P=0.17$ ), though statistical significance was not reached.

There were no other significant differences in characteristics of patients with versus without thrombosis, as shown in Table 5. In addition, there were no significant differences in time-related survival free of transplantation between those patients with and those without thrombosis as shown in Figure 2.

#### Mitral and tricuspid valve function

Initial echocardiographic data regarding mitral valve function were available in 45 patients at a mean interval of  $41\pm 2$  days from initial presentation to The Hospital for Sick Children.

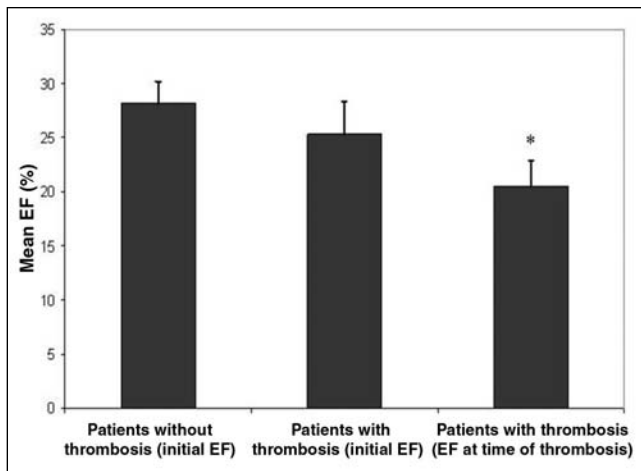


Figure 1) Mean left ventricular ejection fraction (EF). All values are expressed as mean ± SD. \*P<0.05 versus initial EF of patients without thrombosis

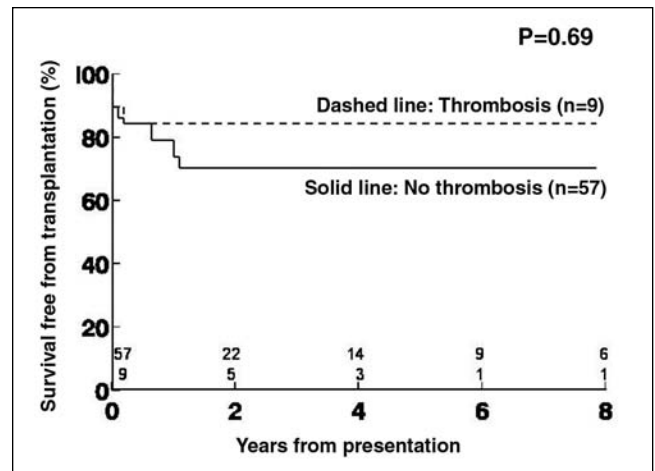


Figure 2) Time-related survival free of transplantation after presentation stratified by the presence of thrombus in patients with dilated and inflammatory cardiomyopathy

TABLE 5  
Comparison of dilated cardiomyopathy patients with thrombus versus without

Patient characteristics	Thrombus absent (n=57)	Thrombus present (n=9)	P
Median age at presentation (range)	2.2 years (1 day to 17.8 years)	2.3 years (birth to 14.3 years)	0.45
Initial ejection fraction, % (mean ± SD)	29±15	24±9	0.42
Initial left ventricular end-diastolic dimension, cm (mean ± SD)	4.57±1.62	4.6±1.63	0.87
Systemic anticoagulation at presentation, %	14	27	0.21
Median follow-up time, years (range)	1.4 (0 to 9.79)	1.2 (1.3 to 9)	0.62

Moderate or greater mitral regurgitation was present in 13 patients (29%). The frequency of important mitral regurgitation was not increased in those presenting with thrombosis (one of four) and those without thrombosis (11 of 41; P=0.74). There was no association between greater than moderate mitral regurgitation and thrombosis formation, and follow-up echocardiography revealed that an additional three patients (one of whom subsequently died) had developed new-onset mitral regurgitation. None of the four patients with thrombosis found on follow-up had important mitral regurgitation. Initial echocardiographic data regarding tricuspid valve function were available in 34 patients. Moderate or greater tricuspid regurgitation was present in five patients (15%) at initial evaluation. Follow-up echocardiography, available in 32 patients, revealed that no patients had important tricuspid regurgitation.

### DISCUSSION

There are numerous reports addressing the natural history and outcomes in children with DCM (1-6). However, specific data on thrombosis and thromboembolism and their impact on outcomes are lacking, and limited to case reports and a single retrospective study (7-9). The overall period prevalence of thrombosis found in the present study was 14%. The reported prevalence of thromboembolism in children with DCM ranges from 4% to 16% (1,4,9), with evidence to suggest that it may be as high as 43% to 57% at autopsy (1,16,17).

There are multiple factors that have been proposed that may predispose patients with cardiomyopathy to thrombosis. These may include impaired LV systolic function, stasis of blood flow, the presence of an abnormal and procoagulant endocardial surface, dysrhythmias and a hypercoagulable state (10-15). Falk et al (10) noted that thrombosis was significantly

more common in patients with a fractional shortening of 10% or less (12 of 15 patients) than in those with a fractional shortening of 11% or more (three of 10 patients; P<0.02). In a series (11) of 103 adult patients with idiopathic DCM (91 without and 12 with LV thrombus), low LV shortening fractions, low LVEFs and greater end-systolic LV dimensions were found to be associated with thrombus formation. Our study failed to show a difference between initial LVEFs for DCM patients with and without cardiac thrombus. However, LVEF at the time of thrombus diagnosis was found to be significantly lower than the initial EF of patients without thrombus. Falk et al (10) also showed that severe mitral regurgitation was present in 12% of those patients without LV thrombus but in no patient with LV thrombus. It was proposed that severe mitral regurgitation prevented LV thrombus formation by reducing stasis and sluggish blood flow (11). We did not observe this association in our population of children.

The criterion standard for diagnosis of intracardiac thrombus is its demonstration at operation or autopsy. While several imaging techniques have been used for its detection (18-25), two-dimensional echocardiography has been shown to be a sensitive (92%), specific (88%), practical and noninvasive bedside tool (22-32) to detect and delineate thrombosis in adults and children with cardiomyopathies (7-9). Diagnostic features described in adults (27), which have been applied and confirmed in children (8), include location of the thrombus most frequently in the ventricular apex, the presence of distinct margins with an acoustic density different from the underlying myocardium, free motion of the intracavitary margin of the thrombus, variation in thrombus characteristics noted on serial examinations and abnormal wall motion of the associated myocardial wall segment. It has been found that

transesophageal echocardiography is superior to transthoracic echocardiography in the detection of intracardiac thrombosis and may be indicated when no intracardiac thrombosis is detected by transthoracic echocardiography in the presence of clinical thromboembolism (9). The main limitation of transesophageal echocardiography is the requirement of general anesthesia in children and the difficulty of examining the cardiac apex, which is a common location for thrombosis.

Systemic anticoagulation with intravenous heparin therapy or oral anticoagulants is indicated when there is evidence of a thromboembolic event and the presence of intracardiac thrombosis. In these situations, antiplatelet therapy alone is inadequate, because it will not promote resolution of the thrombus (8), unlike with systemic anticoagulation (20), which is also felt to be effective in the prevention of thromboembolism (9,20). Clinical thromboembolism without documented intracardiac thrombosis may also warrant anticoagulant therapy. Initiation of anticoagulation therapy is of unknown value in the presence of intracardiac thrombosis without a thromboembolic event, because the susceptibility of asymptomatic intracardiac thrombosis to embolization is unknown (20,21). Current management algorithms do not distinguish between high-risk subgroups, although there have been attempts to define LV thrombosis characteristics that may be associated with a greater embolic risk in adult patients (20,21,30-32). In the absence of such data, there is a trend toward empirical initiation of anticoagulation therapy in the presence of intracardiac thrombosis, especially if the LV shortening fraction is less than 20% (9). Our study failed to identify particular patient characteristics associated with a higher risk of thrombosis. Without identified risk factors, it is not possible to target prophylactic therapy. In addition, anticoagulation therapy is not always effective in preventing thrombosis or recurrence of thromboembolic events in this setting. Our study showed that patients on anticoagulant therapy do not always have their INR or prothrombin time in a therapeutic range. Close monitoring and adjustment of drug dosage is needed to

determine the efficacy of anticoagulant therapy in preventing cardiac thrombus formation in those with DCM. Of the patients in our study who were found to have thrombosis during follow-up or at autopsy, three were on anticoagulation started empirically for poor LV function. However, given the lack of evidence, we continue to recommend routine use of anticoagulation in children with poor ventricular function due to DCM. With improvement of LV function, we recommend discontinuation of anticoagulation. There is no evidence to support a role for antiplatelet therapy. Further trials of both antiplatelet agents and anticoagulation are needed.

### Limitations

The inherent limitations of any retrospective review in a single institution apply to the present report. Specifically, we cannot be certain that all children with DCM and thrombosis were captured because echocardiograms were not rereviewed to look for 'missed thrombi', and transesophageal echocardiography was not used in the majority of our patients. Furthermore, though we have cross-sectional measurements of individual patient INRs, we have no longitudinal data regarding the time in the therapeutic range.

### CONCLUSIONS

Our study suggests that there is a significant yet unpredictable and ongoing risk of thrombosis in children with DCM. However, not all patients with poor LV function develop thrombosis, it may occur despite anticoagulation, and the risk of thromboembolism with asymptomatic thrombosis is unknown. We recommend anticoagulation in children with DCM and thromboembolism, and in the presence of severe LV dysfunction. No risk factors were significantly associated with thrombosis, and it does not appear to be associated with decreased survival free of cardiac transplantation in children with DCM. Therefore, the relevance and prevention of thrombosis in this setting remains unclear.

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