Predictors of thrombotic events in patients with idiopathic inflammatory myopathies

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Abstract

Objective

To identify predictors of thrombotic events in patients with idiopathic inflammatory myopathies (IIM).

Methods

We conducted a retrospective study of a large, longitudinal IIM cohort followed at a single academic centre. We used Poisson regression models to estimate incidence-rate ratios (IRR) of prospective arterial and venous thrombotic events (ATE and VTE respectively).

Results

Thrombotic events occurred in 37 out of 312 patients (12%) over a median [interquartile range (IQR)] follow up time of 6[2-11] years after IIM diagnosis. Among patients with thrombotic events, 65% had VTE, which predominantly occurred within the first 3 years of IIM diagnosis, while 41% had ATE, which predominantly occurred after 10 years from IIM diagnosis. In predictive models, disease duration less than 1 year (IRR 6.49, 95%CI 1.89-22.35) was the strongest risk factor for VTE. Prior ATE was the strongest risk factor for prospective ATE (IRR 18.78, 95%CI 10.98-32.12). Traditional cardiovascular (CV) risk factors and higher levels of myositis activity and damage were other predictors of prospective ATE. The lactonase activity of PON1 was independent of the PON1 Q192R polymorphism and enhanced prediction of ATE in patients with high CV risk. IVIG was not associated with increased thrombotic risk in a high-risk population.

Conclusion

We report the incidence and risk factors for thrombotic events in a single-centre longitudinal IIM cohort, showing early occurrence of VTE and late onset of ATE. PON1 activity was predictive of ATE in a high-risk subgroup of IIM patients.

Key words

idiopathic inflammatory myopathies, cardiovascular disease, stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism

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Introduction

Cardiovascular disease is a leading cause of mortality in patients with idiopathic inflammatory myopathies (IIM) (1, 2). The increased risk of arterial thrombosis in IIM was raised in a Canadian study using provincial healthcare database that reported relative risk of myocardial infarction (MI) to be 1.95 [95%CI 1.35-2.72] compared to age and gender matched general population (3). Since then, a number of studies have supported IIM to be associated with higher incidence rates of MI, stroke, as well as venous thromboembolism including deep vein thrombosis (DVT) and pulmonary embolism (PE) (4-18). The risk became particularly relevant with the approval of IVIG as an effective treatment in IIM by the United States Food and Drug Administration with a black box warning for increased risk of thrombosis (19, 20). Efforts to identify risk factors for arterial or venous thrombosis have suggested a greater prevalence of traditional cardiovascular (CV) risk factors such as hypertension (HTN), diabetes, and hypertriglyceridemia in IIM patients (21, 22) and a recent study showed IIM patients to have significantly increased risk of accelerated subclinical atherosclerosis on carotid ultrasound (23). The relationship between systemic inflammation in rheumatic disease and atherogenesis is well described (24) and recent efforts have elucidated disease specific pathogenetic mechanisms including the crucial role of the interferon pathway which may accelerate complement-mediated angiopathy (25). However, distinct mechanistic pathways in IIM related cardiovascular disease are yet to be discovered, and the predictive role of traditional CV risk factors, disease-related factors and systemic levels of inflammation and oxidative stress in IIM patients remain largely unknown.

In the current work, we conducted a retrospective study of a large, single-centre longitudinal cohort of well-characterised IIM patients to evaluate clinical and laboratory predictors of thrombotic events in IIM. We included evaluation of paraoxonase-1 (PON1), an HDL-associated anti-oxidant protein which is impaired in IIM patients (26). As traditional lipid profiles are often inadequate predictors of thrombotic events in patients with autoimmune disease, we analysed whether the baseline functional and genetic determinants of the PON1 enzyme associated with higher rates of prospective thrombotic events in IIM patients.

Patients and methods

Study population

We evaluated all patients with thrombotic events in a single-centre longitudinal cohort of adult patients with IIM. All patients met EULAR/ACR Classification Criteria for at least "probable" IIM (27) and subclasses including dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM) were verified by chart review. All subjects gave written informed consent for the study approved by the University's Human Research Subject Protection Committee.

Definition of outcomes

All thrombotic events were identified by chart review. Arterial thrombotic events (ATE) included MI and ischaemic cerebrovascular accidents (CVA), while venous thrombotic events (VTE) included deep vein thrombosis (DVT) and pulmonary embolism (PE). Patients had a baseline visit in which predictors were assessed. Patients who had thrombotic events after their baseline visit (*prospective* thrombotic events) were compared to a comparator group of patients that did not have thrombotic events after their baseline visit.

Predictors

Demographic, clinical, laboratory variables and myositis disease-specific measures were collected at the baseline visit. Relevant comorbidities (history of ATE/VTE prior to baseline visit, coronary artery disease [CAD] noted on imaging without a clinical MI, atrial fibrillation, congestive heart failure [CHF], HTN, hyperlipidaemia, diabetes, smoking, cancer, family history of premature MI and CVA) were obtained by questionnaire and chart review. Laboratory studies including inflammatory markers (hsCRP and Westergren ESR),

lipid panel (total cholesterol, quantitative LDL-cholesterol [LDL-C], HDL-cholesterol [HDL-C], triglycerides) were performed by the clinical laboratory using standard methods. Additional blood was collected in heparinised tubes (Becton Dickinson), and plasma stored at -80°C for PON1 assessments. Myositis autoantibodies were analysed by immunoprecipitation or other commercial labs using standardized protocols. Myositis disease activity and damage were assessed by physician (MD) global scores using a 1-100mm visual analog scale (VAS) and a 5-point Likert scale (0-4) (28), serum creatine phosphokinase (CPK) and aldolase. Use of immunomodulatory medications, anticoagulants (warfarin, rivaroxaban, dabigatran, apixaban), aspirin and statins at the time of the visit were collected. The treatment course of IVIG was reviewed in relation to the presence and timing of thrombotic events.

Determination of PON1 activity and PON1 Q192R polymorphism

PON1 activity was quantified using 2 different substrates (dihydrocoumarin and phenylacetate) to assess its lactonase and arylesterase activities respectively (29). The PON1 Q192R polymorphism was determined in IIM patients and controls as described previously (30).

Statistical analysis

Clinical and laboratory variables were compared using student's t-tests or Wilcoxon rank-sum tests for continuous variables, and $\chi 2$ tests or fisher's exact tests for categorical variables.

To assess the predictive value of baseline variables in predicting prospective thrombotic events, we used Poisson regression models to estimate incidence-rate ratios (IRR). Patients with thrombotic events were analysed from their baseline visit until their first prospective ATE or VTE, while patients without thrombotic events were censored at their last follow up visit or death, whichever came first. Each model was adjusted for 1) age, 2) history of prior thrombotic events, 3) baseline global activity VAS. Given the exploratory nature of PON1 activity in relation to the outcome (thrombotic events) in IIM, we first estimated IRR by PON1 activity quartiles before assuming the relationship was appropriate for Poisson regression on a continuous scale.

To assess whether PON1 activity had additional benefit in predicting future thrombotic events beyond traditional CV risk factors, we identified a high-risk subgroup using traditional risk factors that were significant in bivariate comparison and constructed predictive models within this subgroup. We compared the performance of predictive models with and without biomarkers including PON1. Given the small number of events, we utilised factor analysis on traditional lipid levels to reduce the dimensionality and prevent overfit-

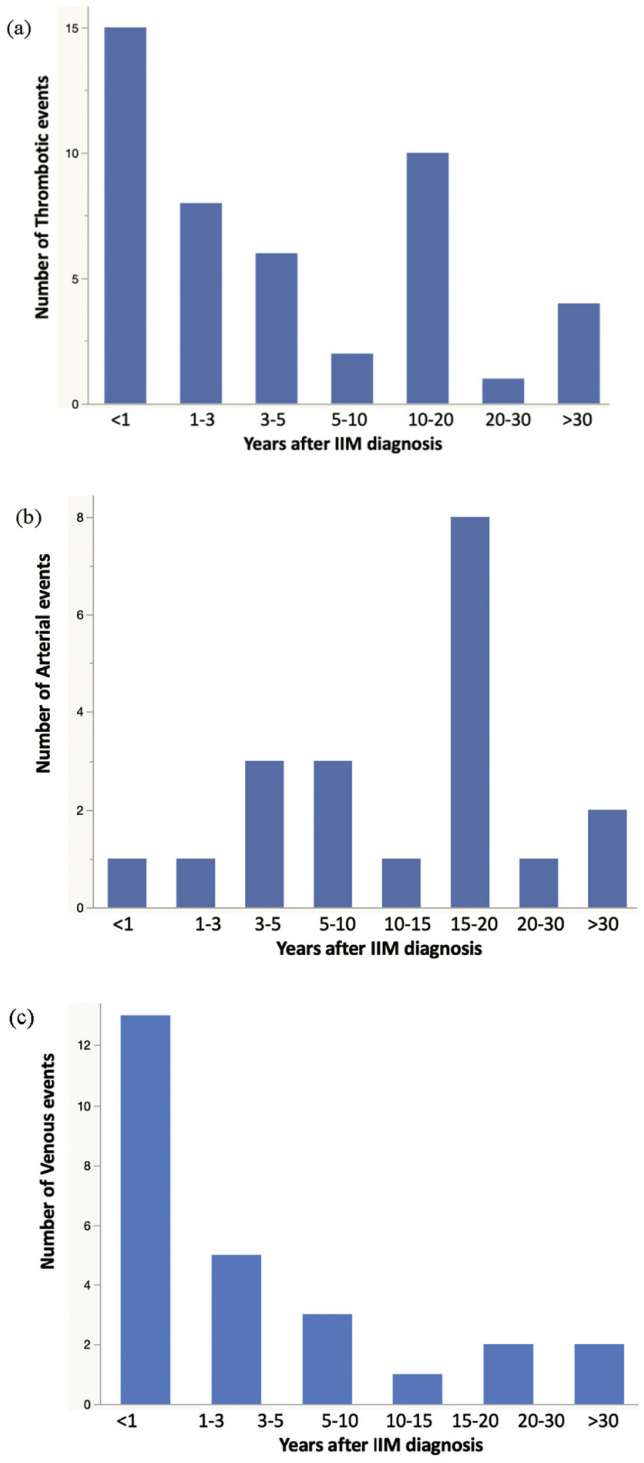

Fig. 1. Timing of thrombotic events after IIM diagnosis.
Number of (**a**) all thrombotic events, (**b**) arterial thrombotic events, (**c**) venous thrombotic events that occurred by IIM disease duration.

ting (31). We used the Akaike Information Criterion (AIC) in which a lower AIC indicates a better fit of the model, to compare model performance (32).
All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA.). All *p*-values are two-sided, with significance level pre-specified at less than 0.05.

Results

Early occurrence of VTE and late occurrence of ATE in IIM patients

We identified a total of 46 thrombotic events in 37 out of 312 patients (12%) that occurred after their IIM diagnosis over a total of 2,567 person-years follow up in the entire cohort [median (interquartile range, (IQR) follow-up time was 6(2-11) years]. The median [IQR] time from IIM diagnosis to thrombotic events was 3[0-13] years and the total event rate was 1.76 events (standard error 0.76) per 100 person-years. Thrombotic events occurred most frequently within the first year of IIM diagnosis (Fig. 1).
Thrombotic events were further divided into arterial (ATE) and venous events (VTE). Fifteen patients (41%) had ATE; 7 events of MI, 13 events of CVA, and 5 patients with more than one ATE. Sixty percent of ATE occurred greater than 10 years after IIM diagnosis. VTE occurred in 24 patients (65%): 21 DVT, 19 PE, and 13 patients with >1 event. Unlike ATE, incidence of VTE had a clear predilection for the first 3 years of IIM (69% of total VTE) and most events occurred within the first year of IIM diagnosis (Fig. 1).

Baseline clinical characteristics of patients with and without prospective thrombotic events

Table I describes baseline characteristics of patients who had prospective thrombotic events (events after baseline visit, n=20, 9 patients with ATE, 13 patients with VTE, 2 patients with both) and comparators (no events after baseline visit, n=292). Patients with prospective thrombotic events were older, had more prior thrombotic events, CAD without MI, and HTN. Traditional lipid profiles were similar in patients with and without prospective thrombotic

Table I. Clinical characteristics of patients with or without prospective thrombotic events (n=312).

	Prospective thrombotic events			No thrombotic event (n=292)
	Total (n=20)	Arterial (n=9)	Venous (n=13)	
Age (at baseline)	**58 ± 13***	**61 ± 13***	54 ± 14	49 ± 16
Sex, female	**10 (50)***	4 (44)	17 (58)	210 (72)
Ethnicity, Hispanic	2 (10)	0	2 (17)	54 (18)
Race, white	11 (55)	4 (44)	7 (58)	181 (62)
Comorbidities				
Cancer, ever	7 (35)	4 (44)	3 (25)	54 (18)
History of MI	1 (5)	1 (11)	0	3 (1)
History of CVA	**2 (10)***	**2 (22)***	0	4 (1)
History of MI or CVA	**3 (15)***	**3 (33)***	0	7 (2)
History of DVT/PE	**4 (20)***	1 (11)	**4 (33)***	14 (5)
CAD without MI	**6 (30)***	**4 (44)***	2 (17)	32 (11)
Atrial fibrillation	1 (5)	0	1 (8)	14 (5)
Heart failure	1 (5)	1 (11)	0	7 (2)
HTN	**12 (60)***	**6 (67)***	6 (50)	78 (27)
HLD	5 (25)	2 (22)	3 (25)	61 (21)
Diabetes	6 (30)	**5 (56)***	1 (8)	38 (13)
Obesity (BMI≥30)	3 (15)	1 (11)	2 (20)	81 (33)
FHx of premature MI§	4 (20)	0	**4 (40)***	31 (13)
FHx of premature CVA§	1 (5)	1 (17)	0	10 (6)
Smoking, ever	7 (39)	**5 (56)***	3 (30)	57 (22)
Lipids†				
Total cholesterol	215 ± 52	232 ± 54	211 ± 57	208 ± 54
LDL-C	124 ± 40	131 ± 48	115 ± 28	122 ± 48
HDL-C	54 ± 25	53 ± 28	53 ± 24	63 ± 29
Triglyceride	200 ± 168	233 ± 231	227 ± 205	173 ± 166
Labs†				
hsCRP	3.3 [0.7-11.5]	4 [0.9-22]	3.0 (0.6-18.7)	1.6 [0.6-5.3]
ESR	33 [14-56]	38 (19-76)	28 (13-47)	22 [9-42]
CPK	118 [78-541]	90 [148-672]	95 (61-804)	119 [62-347]
Aldolase	6.9 [4.7-12.5]	6.7 [4.0-10.9]	7.2 (4.4-13)	6.3 [4.7-9.6]
PON1 activity‡				
Arylesterase	186 ± 53	**172 ± 36***	197 ± 59	202 ± 82
Lactonase	17 ± 8	**12 ± 3***	20 ± 8	17 ± 7
PON1 Q192R genotype‡				
QQ	6 (30)	2 (25)	4 (33)	82 (35)
QR	6 (30)	4 (50)	2 (17)	123 (52)
RR	4 (20)	2 (25)	3 (25)	31 (13)
Medications				
Aspirin	6 (32)	**4 (44)***	2 (18)	45 (15)
Statin	2 (10)	1 (11)	1 (8)	37 (13)
Anticoagulants	1 (5)	1 (11)	1 (9)	8 (3)
IVIG	3 (15)	1 (11)	2 (17)	89 (31)
Mycophenolate	4 (20)	3 (33)	2 (17)	97 (33)
Rituximab	4 (20)	2 (22)	3 (25)	32 (11)
Cyclophosphamide	1 (5)	1 (11)	0	13 (4)
Azathioprine	2 (10)	1 (11)	1 (9)	29 (10)
Methotrexate	6 (30)	2 (22)	5 (42)	62 (21)
Hydroxychloroquine	4 (20)	2 (22)	3 (25)	54 (19)
TNF inhibitor	0	0	0	6 (2)
Prednisone	16 (80)	8 (89)	9 (75)	198 (68)
Prednisone dose, mg/day, median[IQR]	20 [5-40]	18 [5-48]	25 [1-55]	10 [1-25]
IIM type, dermatomyositis	13 (65)	5 (55)	8 (67)	214 (73)
Antisynthetase	3 (15)	1 (11)	2 (15)	50 (17)
IMNM	1 (5)	1 (11)	1 (8)	31 (11)
Inclusion body myositis	0	0	0	17 (6)

Cont.ed Table I

	Prospective thrombotic events			No thrombotic event (n=292)
	Total (n=20)	Arterial (n=9)	Venous (n=13)	
Myositis autoantibodies[¶]				
Antisynthetase ab	3 (15)	1 (11)	2 (17)	49 (17)
MDA5 ab	0*	0	0	29 (10)
SRP ab	1 (5)	1 (11)	1 (8)	22 (8)
HMGCR ab	0	0	0	7 (2)
Mi2 ab	1 (5)	0	1 (8)	12 (4)
TIF1 gamma or p155/140	3 (15)	1 (11)	2 (17)	35 (12)
NXP2 ab	1 (5)	1 (11)	0	13 (4)
RNP ab	0	0	0	4 (1)
Ro ab	1 (5)	0	1 (8)	13 (4)
SAE ab	0	0	0	5 (2)
Ku ab	0	0	0	4 (1)
PM-Scl ab	0	0	0	6 (2)
Unidentified ab	3 (15)	2 (22)	1 (8)	18 (6)
None	2 (10)	1 (7)	1 (8)	13 (4)
Interstitial lung disease	7 (35)	4 (44)	3 (25)	97 (35)
MD global VAS (1-100mm)	51 ± 25	51 ± 27	51 ± 23	41 ± 21
MD global likert (0-4)	2.1 ± 0.8	2.1 ± 0.9	2.1 ± 0.8	1.8 ± 0.8
MD damage VAS (1-100mm)	36 ± 21	43 ± 26	30 ± 14	32 ± 22
MD damage likert (0-4)	1.8 ± 0.9	2.1 ± 1.0	1.5 ± 0.5	1.5 ± 0.9
Disease duration at baseline visit, months	7 [0.5-76]	11 [5-83]	3 [0-43]	15 [3-58]
Follow up time after baseline, months	65 [27-98]	69 [43-102]	54 [13-112]	33 [9-82]

Values are n(%) or mean ± SD unless specified.
Prospective thrombotic events are defined as ATE and/or VTE that occurred AFTER baseline visit in which predictor variables were collected.
*p<0.05 compared to No thrombotic events group.
Continuous variables with normal distribution are presented as means with standard deviation, and skewed variables are presented as medians with interquartile range (IQR).
[§]Fhx of premature MI and CVA were defined by events occurring before the age of 55 for men and 65 for women in first degree relatives.
† Lab data missing in 10 patients; lipid panel missing in 14 patients
‡PON enzyme activity missing in 7 patients (all in No event group), genotype missing in 60 patients (4 in Event group, 56 in No event group).
[¶]Myositis autoantibody assessments were available for 246/312 IIM patients (170 analysed by immunoprecipitation and 76 analysed in commercial labs).
MI: myocardial infarction; CVA: cerebrovascular accident (ischaemic); DVT: deep vein thrombosis; PE: pulmonary embolism; CAD: coronary artery disease; HTN: hypertension; HLD: hyperlipidaemia; Fhx: family history; IVIG: intravenous immunoglobulin; VAS: visual analog scale.

events. Comparison within myositis antibody subgroups was limited due to the small number of events.

Patients with prospective ATE were older, had more prior ATE (but not VTE), CAD without MI, HTN, diabetes, smoking history, and more use of aspirin than the comparator group at baseline. Patients with prospective VTE (n=12) had more prior VTE but no association was noted with age or prior ATE. Bivariate analysis at the baseline visit did not reveal associations with myositis disease-specific measures or medications.

Evaluation of predictors of prospective thrombotic events in IIM patients

In order to estimate the predictive value of baseline variables, we used Poisson regression models to estimate IRR of prospective thrombotic events. Results of age-adjusted models are presented in Figures 2 and 3. The full list of predictors, unadjusted models and models adjusted for history of prior thrombotic event, or baseline myositis disease activity are presented in Supplementary Tables I and II.

ATE. A total of 9 patients had 12 events of prospective ATE (Fig. 2). Patients with prior ATE (n=10) had the highest risk of a recurrent prospective ATE (IRR[95%CI] 18.8 [11.0-32.1], p<0.01). Traditional CV risk factors including older age, male sex, CAD without MI, CHF, HTN, diabetes, smoking, lipid levels, and family history of premature stroke (but not MI), and aspirin use were associated with higher rates of prospective ATE in all models (age-adjusted model in Figure 2, unadjusted, adjusted for prior ATE, adjusted for MD global activity VAS models in Supplementary Table S1). In models adjusted for prior ATE, statin use was associated with lower rates of ATE. A history of cancer was associated with ATE in the unadjusted model, but did not remain significant once adjusted for age. Models adjusted for MD global activity VAS identified similar significant variables as the age-adjusted model (Supplementary Table S1).

Among myositis-related variables, higher baseline global activity and damage scores (VAS>50) and higher CPK were associated with higher rates of prospective ATE. DM patients had lower rates of prospective ATE compared to PM and IBM patients in the unadjusted model but this finding was no longer significant after adjustment for age or prior ATE. Rituximab, cyclophosphamide and prednisone use at baseline were associated with higher rates of prospective ATE. Myositis autoantibodies and IIM disease duration were not significant predictors of prospective ATE (Fig. 2, Supplementary Table S1).

VTE. Prospective VTE were observed in 13 patients (15 events) (Fig. 3). Disease duration of less than 1 year was the strongest predictor of prospective VTE among all predictors (IRR[95%CI] 6.5[1.9-22.4], p<0.01) (Fig. 3). Older age, previous VTE and ATE, HTN, family history of premature MI (but not CVA) were predictive of prospective VTE in all tested models (Fig. 3, Supplementary Table S2). Traditional lipids, cancer, and atrial fibrillation were not associated with prospective VTE.

Higher baseline myositis global activity (VAS>50, but not damage), rituximab and methotrexate use were associated with higher rates of prospective VTE. IIM disease subtype, myositis autoantibodies, ILD, and IVIG use were not associated with prospective VTE.

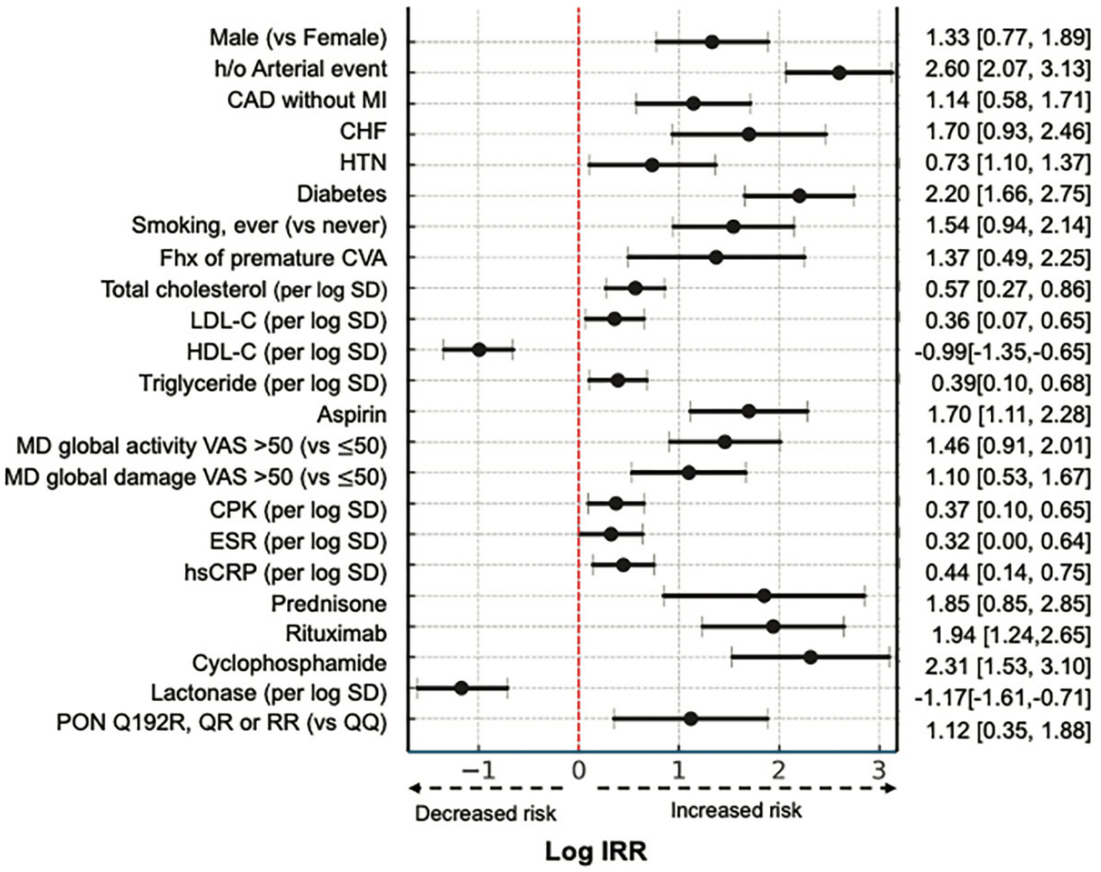

Fig. 2. Clinical and laboratory predictors of ATE using Poisson regression models (adjusted for age).
Model estimates are reported as log transformed incidence rate ratios (IRR) of ATE that happened after baseline visit. Presented only predictors that are significant in age-adjusted model. For full list of predictors and other models adjusted for prior ATE and for MD global disease activity see Supplementary Table S1.

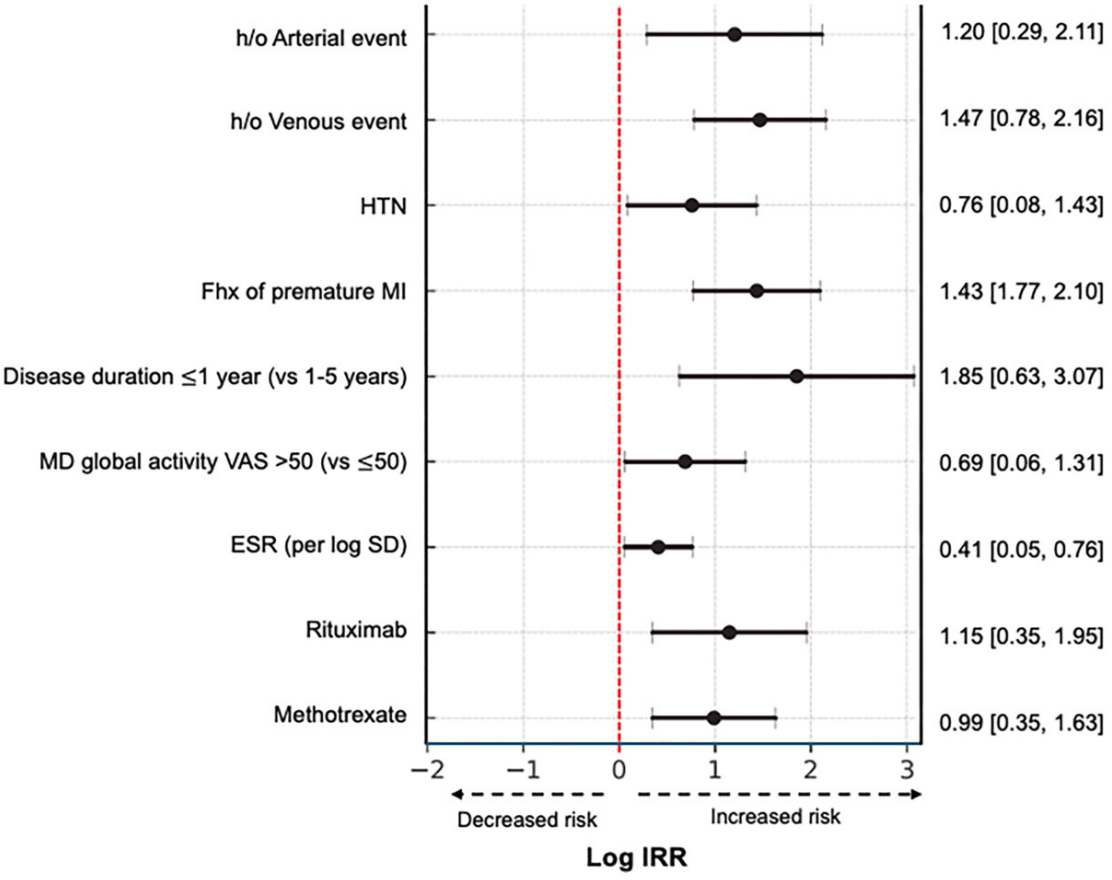

Fig. 3. Clinical and laboratory predictors of VTE using Poisson regression models (adjusted for age).
Model estimates are reported as log transformed incidence rate ratios (IRR) of VTE that happened after baseline visit. Presented only predictors that are significant in age-adjusted model. For full list of predictors and other models adjusted for prior ATE and for MD global disease activity see Supplementary Table S2.

Association of thrombotic events with measures of systemic inflammation and oxidative stress

Higher levels of systemic inflammation measured by ESR and hsCRP associated with prospective ATE (Fig. 2, 3). Higher ESR, but not hsCRP, was also associated with prospective VTE.

The baseline lactonase activity of PON1 was significantly lower in all patients with prospective ATE compared patients no prospective ATE (Table I). Patients were divided into quartiles by baseline PON1 activity levels, and lower lactonase quartiles associated with increased rates of prospective ATE, while arylesterase quartiles did not. (Supplementary Table S3a for lactonase, S3b for arylesterase). The association between lower lactonase with increased rates of prospective ATE was statistically significant in Poisson models with lactonase on a continuous scale and remained significant in models adjusted for age, prior ATE, or myositis disease activity (Fig. 2, Supplementary Table S1). Patients with RR or QR genotypes of the PON1 Q192R polymorphism had 2.6[1.1-5.8] times the incidence rate of prospective ATE compared to patients with the QQ genotype (p=0.02); this association remained statistically significant (p=0.004) in age-adjusted models (Fig. 2).

Baseline PON1 activity and genotype were similar in VTE cases and comparators (Table I). When patients were divided by lactonase quartiles IRR for prospective VTE, lactonase activity did not follow a trend but rather fluctuated inconsistently across quartiles (Supplementary Table S3). Therefore, lactonase was not modelled on a continuous scale.

Suppressed PON1 activity predicts ATE in high CV risk group

Patients with a history of prior ATE at baseline had the highest rates of prospective ATE (Fig. 2). Other high-risk clinical features associated with prospective ATE included CAD without MI, HTN, CHF, diabetes, and smoking. In order to evaluate whether lactonase added benefit in CV risk stratification, we identified a high CV risk subgroup and evaluated all prospective ATE that occurred in this subgroup. Three separate Poisson models for prospective ATE were constructed to assess the value of adding biomarkers in predicting prospective ATE (Table II): model 1 used factor scores derived from traditional lipids, model 2 used PON1 lactonase activity, and model 3 used hsCRP. Compared to the null model, the addition of PON1 by lactonase (model 2) significantly improved the prediction of prospective ATE within the high CV risk subgroup. In fact, the lactonase model (model 2) had the best model performance in predicting prospective ATE and was significantly better than model 1 or 3.

Table II. Poisson regression models for prospective ATE in high CV risk subgroup (n=125).

	Parameter	IRR	*p*-value	AIC
Model 1	Factor 1 (Total cholesterol, LDL) Factor 2 (HDL, triglyceride)	1.31[0.74-1.73] 0.60[0.35-1.02]	0.57 0.06	82.1
Model 2	Lactonase	**0.86[0.79-0.93]**	**0.0003**	**65.9**
Model 3	hsCRP	1.04[1.01-1.07]	0.18	81.4

Total high CV risk subgroup was 145 patients in which all 12 prospective ATE events (9 persons with events) occurred. Analysis was performed in 125 patients (11 events, 8 persons with event) with complete biomarkers in order to compare model performance within the same sample size.
Poisson regression models used to estimate the ratio of expected number of events for a unit increase in predictor variable (IRR, incidence rate ratio).
P-value by likelihood ratio test to compare the performance of each model (models 1-3) against a null model (a model with no additional biomarker predictors).
AIC (Akaike Information Criterion) to compare the model performance of predicting prospective ATE. Lower AIC indicates a better fit, and greater than 2 point decrease in AIC indicates significantly improved model performance (32).
Model 1 used factor scores derived from factor analysis using traditional lipids.

Safety of IVIG in patients with history of prior thrombotic events

IVIG at baseline visit was not associated with higher rates of future thrombotic events (Table I, Fig. 2, 3). In fact, baseline use of IVIG was associated with reduced risk of future ATE in all regression models except the age-adjusted model. (Supplementary Table S2). There was no association of IVIG with prospective VTE at baseline or in Poisson models (Fig. 2, Supplementary Table S1).

Because patients may have been using IVIG at some point even if they were not on IVIG at the baseline visit, we identified all patients that ever received IVIG during longitudinal follow-up (n=199), and found that 11(6%) patients had events while on IVIG (7 ATE, 5 VTE). This was in comparison to 113 patients that never received IVIG among which 11(10%) had events (5 ATE, 6 VTE) after IIM diagnosis. The odds for thrombotic events were not significantly increased in patients ever on IVIG compared to patients never on IVIG (OR 0.56 [0.23-1.34], p=0.20 for all events, OR 1.19[0.44-3.25] p=0.74 for ATE and OR 1.19[0.52-2.74], p=0.68 for VTE).

As patients with history of prior thrombotic events had the highest rates of prospective events and there may be concern for IVIG use in these high-risk patients, we also analysed patients that received IVIG after a prior ATE or VTE (n=24, Table III). IVIG was safely tolerated in 20/24(83%) patients for a median (IQR) duration of 23(10-74) months. Two patients discontinued IVIG after an additional thrombotic event (both CVA). One patient had an MI but continued IVIG and tolerated it well without additional thrombotic events for 35 months after the MI. One patient had a single IVIG treatment and had an unrelated CVA and DVT 6 years later. Among the patients with prior thrombotic events who never received IVIG (n=15) there was 1 patient (7%) that had an additional thrombotic event. Among patients with prior thrombotic events, the odds for additional thrombotic events were not significantly increased in those who received IVIG compared to those who did not receive

Table III. IVIG use in patients with a history of prior thrombotic events.

Age/sex	First thrombotic event	Risk factors	IVIG dose/ regimen	Duration of IVIG after event (months)	Additional thrombotic event after IVIG	Comments
68/F	DVT/PE, AMI, CVAx2	HTN, diabetes, DCIS on hormone therapy, known atherosclerosis	1.5g/kg q1m	29	CVA	Held for 8 months after CVA, 2-month trial of subcutaneous treatment then deceased after DVT/PE
71/M	AMI	Diabetes	0.5g/kg qwk (3/4wk)	7	CVAx2	Held after first CVA, had recurrent CVA 5 months after last IVIG infusion
52/M	AMI, CVA	HTN, HLD, diabetes	2g/kg q2-3m	35	AMI	Continued at last f/u
36/F	DVT/PE	SLE, APLS	2g/kg once	1	CVA, DVT	1 course of IVIG. Had CVA and DVT 6 years after IVIG infusion
47/F	DVT/PE	Antiphospholipid syndrome	0.5g/kg qwk	173		Continued at last f/u
52/F	DVT/PE	HTN, HLD	1g/kg q3wk	111		Continued with SQIG
79/F	DVT/PE	May Thurner syndrome, HTN, HLD	2g/kg q1m	34		Disease remission
70/F	PE	Antithrombin III deficiency, HTN, HLD	0.5g/kg q1m	73		Continued at last f/u
36/M	DVT/PE		2g/kg q1m	14		Continued at last f/u
36/M	DVT/PE	CHF, HTN, diabetes	0.5g/kg once	1		Disease remission
52/F	CVA		2g/kg q1m	77		Continued at last f/u
71/M	AMI		0.25g/kg qwk	12		Continued at last f/u
49/F	DVT	Clotted IV catheter	0.5g/kg qwk (3/4wk)	38		Continued at last f/u
53/F	CVA		0.5g/kg qwk	13		Continued at last f/u
73/F	DVT	HLD, obesity	0.4g/kg qwk	10		Continued at last f/u
47/M	DVT/PE mult.	Factor V Leiden, HTN	0.5g/kg qwk	32		Continued at last f/u
56/F	PE		0.5g/kg qwk	7		Continued at last f/u
65/M	DVT		0.3g/kg qwk	1		Continued at last f/u
46/M	DVT/PE		1.7g/kg q1m	12		Continued at last f/u
41/F	DVT	Hospitalisation	0.3g/kg qwk	95		Continued at last f/u
69/F	CVA		2g/kg q1m	101		Continued at last f/u
61/M	AMI		0.5g/kg qwk	45		Switched to SCIG
72/M	CVA		0.5g/kg qwk	1		Continued at last f/u then lost to f/u
57/F	AMI	CAD, hyperlipidaemia	0.5g/kg qwk	10		Switched to SCIG

Age at start of IVIG after thrombotic event. Duration of IVIG after thrombotic event.
DCIS: ductal carcinoma in situ of breast; APLS: antiphospholipid syndrome; SLE: systemic lupus erythematosus; DVT: deep vein thrombosis; PE: pulmonary embolism; AMI: acute myocardial infarction; CVA: cerebrovascular accident (ischaemic stroke); SCIG: subcutaneous immunoglobulin.

IVIG (OR 2 [0.19-21.23], p=0.55).
Baseline lactonase activity in the 3 patients that had additional thrombotic events (all ATE) after IVIG (10.8[9.1-11.3], median [IQR]) were significantly lower than patients with prior thrombotic events that did not have additional thrombotic events on IVIG (17.3 [12.5-25.4], p=0.049).

Discussion

The current work is the first study to comprehensively evaluate associations of demographic characteristics, traditional cardiovascular risk factors, IIM disease-related factors and markers of systemic inflammation and oxidative stress with the risk of prospective ATE and VTE in IIM patients.

Thrombotic events were observed in 12% with a slight predominance of VTE (57%) compared to ATE (43%) in our cohort. Early thrombotic events were more likely VTE, while most ATE occurred between 10-20 years after IIM diagnosis. The early occurrence of VTE post IIM diagnosis is consistent with prior studies (17, 33, 34), while the timing of ATE is more variable between studies. A Taiwanese population-based study demonstrated significantly greater risk of acute coronary syndrome in patients with >5year follow up than those with shorter follow up (12), whereas other studies report higher rates of ATE within the first 5 years of IIM and rates decreasing thereafter (11, 13). Some of the variation in timing of ATE may be due to difference in the definition of events or the methodology used to identify events.

A recent meta-analysis reported an increased relative risk of overall thrombotic events by 2.37(95%CI 1.86-3.02) in DM and PM compared to the general population, and traditional CV risk factors including older age, HTN and previous events were associated with higher risk (16). In the current work, we also observed associations of traditional CV risk factors with prospective ATE. A Taiwanese nationwide study demonstrated that IIM patients with comorbidities such as HTN, diabetes, hyperlipidaemia, stroke, COPD and ESRD had greater hazard ratios of

acute coronary syndrome (15), while a Swedish cohort showed no association with traditional CV risk factors except older age (17). A possible explanation for the variation in results may be the use of time-dependent analysis which may provide additional power to detect differences between groups. Also, the relationship with ATE that may occur later in the disease course can be missed if follow-up time is not considered.

Higher baseline myositis disease burden by global disease activity and damage scores and CPK levels were also risk factors for prospective ATE in the current study. Medications that are used for patients with high disease activity such as rituximab and cyclophosphamide associated with prospective ATE, further supporting that patients with high disease burden at baseline are at higher risk of prospective ATE. Steroids are a commonly used first-line agent for IIM treatment and those with greater disease burden frequently require higher cumulative doses, which is a known independent risk for ATE (35). However, the current analysis is unable to discern whether these medications represent the severity of IIM or an independent risk factor for ATE. On the other hand, VTE clearly associated strongly with shorter disease duration, but its association with myositis disease burden was weaker than ATE.

Arterial and venous thrombosis are distinct in pathophysiology (36) which may explain their discrepant association with higher myositis disease burden. Arterial thrombi are usually superimposed to atherosclerotic plaques, sites of chronic vascular inflammation, whereas venous thrombus formation occur at sites where blood flow is static and there is imbalance in haemostasis but the vein wall is undamaged (36). Therefore, statins, which stabilise atherosclerotic plaques over time are used in ATE, while anticoagulants are the mainstay of therapy in VTE. In IIM, vasculopathy plays a crucial role in disease pathogenesis. We hypothesize that patients with higher myositis disease burden may perpetuate endothelial damage and vasculopathy over time which serves as an additional risk factor for prospective ATE that occur later in the disease course. On the other hand, the onset of myositis and its associated inflammatory state may directly influence the Virchow triad, venous stasis and hypercoagulability leading to early occurrence of VTE.

There is substantial interest in the use of biomarkers to identify persons at risk for future thrombotic events who may be targeted for risk reduction. High total cholesterol, LDL-C, triglycerides and low HDL-C are well described risk factors for ATE but not VTE (36) which was also true in our IIM cohort. PON1, which metabolizes pro-inflammatory oxidized lipids, preventing LDL oxidation and atherosclerotic plaque development, has been proposed as a novel biomarker of CV risk, particularly in patients for whom traditional CV biomarkers such as lipid levels do not adequately risk stratify (37, 38). In our IIM cohort, low lactonase activity of PON1 and non-QQ genotype of Q192R polymorphism were associated with higher rates of prospective ATE independent of age, history of prior ATE, or myositis disease activity. In patients with high CV risk features, the lactonase activity of PON1 enhanced the prediction of prospective ATE and was more accurate than traditional lipids or hsCRP. This work is consistent with data in non-IIM cohorts (37, 39, 40), suggesting that PON1 may warrant further investigation as a biomarker to identify IIM patients at highest risk for prospective ATE.

Statins reduce CV risk proportional to the patient's underlying CV risk, meaning that patients with high baseline CV risk will have the most benefit from statins (41). In the current analysis, statin use was significantly associated with reduced future ATE risk when adjusted for prior ATE, and also trended towards reducing risk in all other models. Our previous work has suggested that statins are well tolerated in IIM patients without HMGCR autoantibodies (42).

Unlike ATE, VTE was not associated with lower lactonase activity. Very few studies report the association between PON1 and VTE, and results are conflicting (43, 44). As VTE is caused by a distinct physiology than ATE, the impact of PON1 on VTE may be different from ATE and warrants further evaluation.

IVIG is approved for use in DM but carries a black box warning for increased risk of thrombosis (19, 20). We explored the safety of IVIG use in patients at the highest risk for thrombosis due to a history of prior events. While IVIG was safely tolerated in 83% of patients, there were 3/24 patients that had additional thrombotic events. However, the odds for additional thrombotic events were not significantly increased for those patients who received IVIG after prior thrombotic event compared to those who never received IVIG after a thrombotic event. It is important to note, patients with prior events were managed collaboratively with a cardiologist with particular attention to slow infusion rates and close monitoring in order to mitigate the increased thrombotic risk of continuing IVIG. Interestingly, the patients with additional future ATE on IVIG had significantly lower baseline lactonase activity of PON1, further supporting more investigation of this enzyme in risk stratification of prospective ATE in IIM.

Our study has several limitations. Although our study cohort is a substantial number for a rare disease, the number of thrombotic events were low. We used time-dependent models to improve the power to detect significant associations, but our ability to perform robust multivariate adjustments including assessments in myositis antibody subgroups was limited. Potential confounders such as prolonged immobility and presence of concurrent antiphospholipid antibodies were not addressed. Also, patients were from a single academic centre in the United States which may limit the generalisability of our findings in terms of ethnicity, disease severity and access to care. Lastly, predictors were only assessed at baseline visit and may have shown different associations had they been assessed at the time of the event. For example, treatment variables including prednisone dose were collected at baseline visit when PON1 levels were assessed, but may have changed dur-

ing the follow up time. Our analysis is unable to discern whether associations with treatment was due to the medication itself, or unmeasured confounders such as cumulative steroid dose or certain disease phenotypes that warranted certain treatments.

In conclusion, we report the incidence and risk factors for ATE and VTE in a single-centre IIM cohort. ATE occurred late in the disease and was associated with traditional CV risk factors such as prior ATE, older age as well as higher myositis disease burden. Low lactonase activity of PON1 was predictive of prospective ATE, and added predictive value of prospective ATE in high CV risk patients. Risk factors for VTE included shorter disease duration, older age and previous VTE. Future multicentre studies with larger numbers of events are warranted to confirm our findings and perform robust model adjustments for potential confounders as well as study the impact of risk reducing interventions.

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