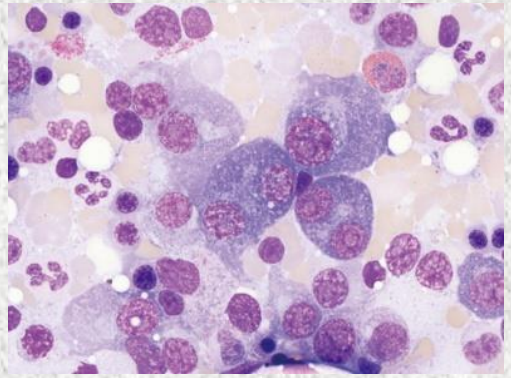
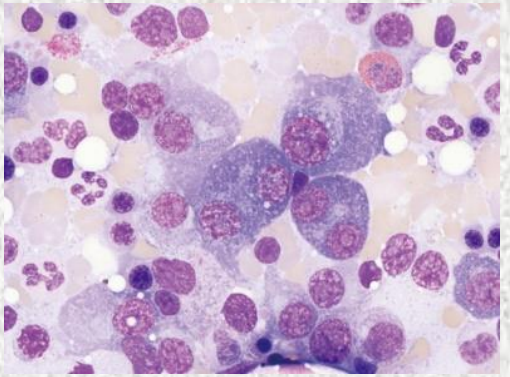
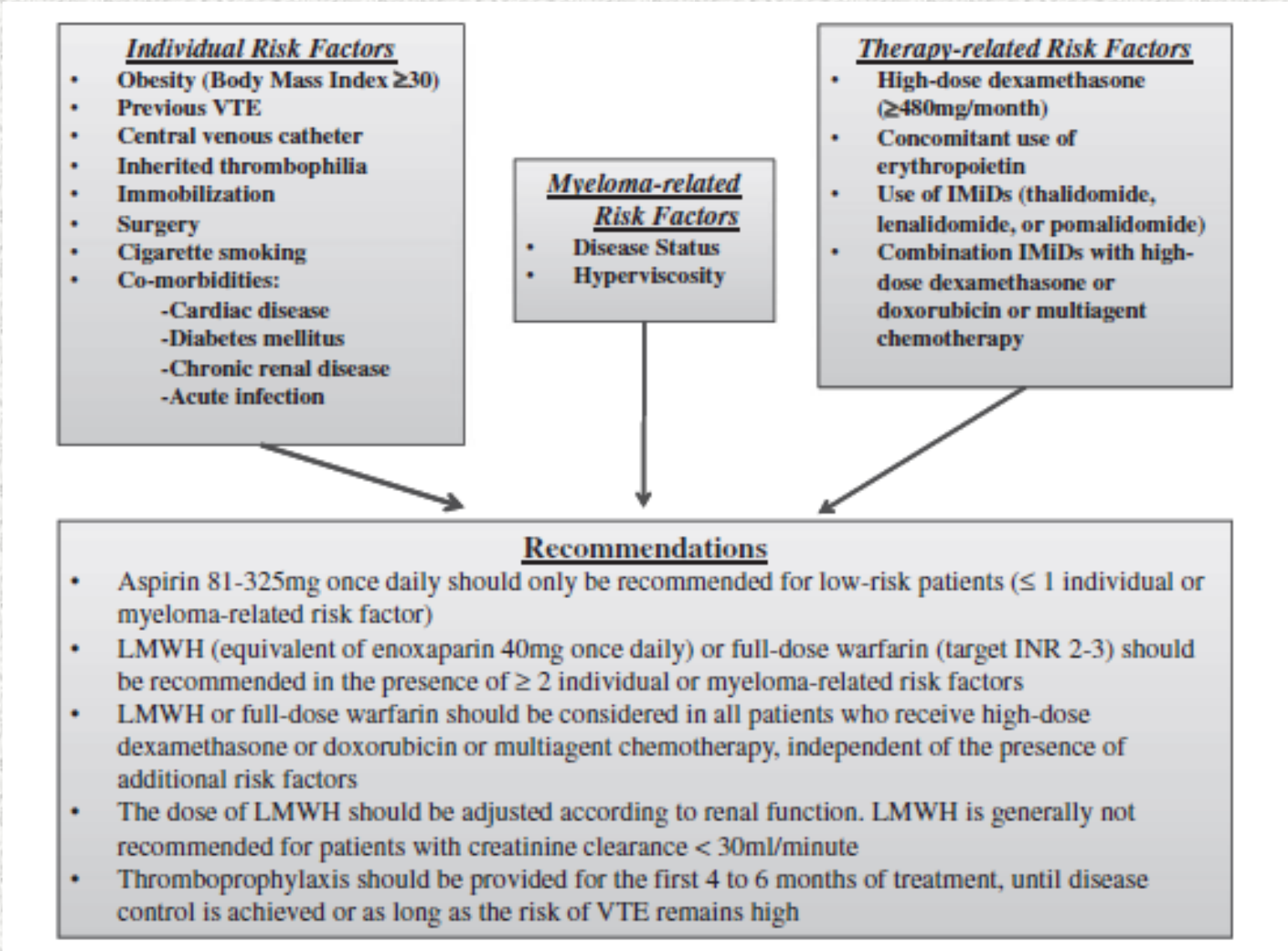
Plazma Hücre Hastalıkları ve Tromboz Sorunu

Nil GÜLER







Circulation 2016;133:908-912

Hastalık ve Tedavi ilişkili Faktörler

- Hasta ilişkili
- Tedavi ilişkili
- Myeloma ilişkili

Kişisel Risk Faktörleri

NCCN

Obezite (BMI ≥ 30)

Önceki VTE

Santral Venöz Katater

Kalıtsak Trombofili

Hareketsizlik

Cerrahi

Trombotik hastalıklar

Kalp Hastalığı

Diabetes Mellitus

Kronik Böbrek Hastalığı

Akut İnfeksiyon

Sigara

Travma

Anestezi

ORIGINAL RESEARCH

Derivation and Validation of a Risk Assessment Model for Immunomodulatory Drug–Associated Thrombosis Among Patients With Multiple Myeloma

Ang Li, MD[a]; Qian Wu, PhD[b]; Suhong Luo, MS[c]; Greg S. Warnick[d]; Neil A. Zakai, MD[e]; Edward N. Libby, MD[f]; Brian F. Gage, MD, MSc[g]; David A. Garcia, MD[a]; Gary H. Lyman, MD, MPH[d,f]; and Kristen M. Sanfilippo, MD, MPHS[c,g]

© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 17 Issue 7 | July 2019

lit-102

Table 3. Derivation and Validation of SAVED Score Using Multivariable Cox Regression Analysis

Variable	Derivation Cohort (SEER-Medicare) HR	Derivation Cohort (SEER-Medicare) *P* Value	Validation Cohort (VHA) HR	Validation Cohort (VHA) *P* Value	Point[a]
Surgery (within 90 days)	1.74	.15	2.30	.05	+2
Asian race	0.26	<.01	0.43	.40	−3
VTE history	3.03	<.01	4.65	<.01	+3
Eighty (age ≥80 y)	1.54	<.01	0.75	.26	+1
Dexamethasone dose					
Standard dose (120–160 mg)	1.36	.05	1.18	.50	+1
High dose (>160 mg)	1.58	.02	2.41	<.01	+2
Risk stratification[b]	HR (high/low) = 1.85 (*P*<.01)		HR (high/low) = 1.98 (*P*<.01)		High if ≥2
	c-index = 0.61 (95% CI, 0.57–0.64)		c-index = 0.60 (95% CI, 0.54–0.64)		

SEER n: 2.397

VHA: n: 1.251

RAM: Risk assessment model

lit-102

Table 3. Derivation and Validation of SAVED Score Using M

Variable	Derivation Cohort (SEER-Medicare) HR	P Value
Surgery (within 90 days)	1.74	.15
Asian race	0.26	<.01
VTE history	3.03	<.01
Eighty (age ≥80 y)	1.54	<.01
Dexamethasone dose		
Standard dose (120–160 mg)	1.36	.05
High dose (>160 mg)	1.58	.02
Risk stratification[b]	HR (high/low) = 1.85 (P<.01)	
	c-index = 0.61 (95% CI, 0.57–0.64)	

lit-102

Table 3. Derivation and ivariable Cox Regression Analysis

Variable	Validation Cohort (VHA) HR	*P* Value	Point[a]
Surgery (within 90 days)	2.30	.05	+2
Asian race	0.43	.40	−3
VTE history	4.65	<.01	+3
Eighty (age ≥80 y)	0.75	.26	+1
Dexamethasone dose			
Standard dose (120–160 mg)	1.18	.50	+1
High dose (>160 mg)	2.41	<.01	+2
Risk stratification[b]	HR (high/low) = 1.98 (*P*<.01)		High if ≥2
	c-index = 0.60 (95% CI, 0.54–0.64)		

lit-102

NCCN

	HR	Risk Stratification	VTE Incidence (95% CI)		
			3 mo	6 mo	12 mo
SEER-Medicare	1.21 (P=.17)	High (n=1,023)	5% (4–7)	9% (7–12)	15% (12–19)
		Low (n=1,374)	5% (4–6)	8% (7–10)	11% (9–13)
VHA	1.41 (P=.07)	High (n=587)	5% (4–7)	9% (7–12)	13% (10–16)
		Low (n=664)	4% (3–6)	8% (6–10)	9% (7–11)

SAVED RAM

	HR	Risk Stratification	VTE Incidence (95% CI)		
			3 mo	6 mo	12 mo
Derivation	1.85 (P<.01)	High (n=686)	7% (6–10)	12% (10–16)	19% (15–24)
		Low (n=1,711)	4% (3–5)	7% (6–9)	10% (8–12)
Validation	1.98 (P<.01)	High (n=414)	6% (4–9)	11% (9–15)	16% (12–20)
		Low (n=837)	4% (3–6)	7% (5–9)	8% (6–10)

bjh correspondence

Retrospective study of the incidence and patterns of arterial and venous thrombosis in Chinese *versus* African American patients with multiple myeloma

Çinli hastalarda VTE sıklığı

African American'lardakinden çok düşük (%3.3 vs 22)

Lit-26

British Journal of Haematology 2017;176:315-330

Low incidence of thromboembolism in relapsed/refractory myeloma patients treated with thalidomide without thromboprophylaxis in Taiwan

Tayvan serisinde VTE insidansı %3.5

Profilaksi oranı %6.1

Lit-38

Ann Hematol 2012;91:1773-1778

Table 2 Venous thromboembolism frequency in relapsed/refractory myeloma patients treated with thalidomide-based regimen in Taiwan and Western countries

		Thromboprophylaxis, *n* (%)	VTE, *n* (%)
Thal alone	Western [21] (*N*=373)	134 (36)	12 (3.2)
	Taiwan Series (*N*=52)	0	0
Thal/Dexa	Western[a] (*N*=91)	0	7 (7.7)
	Taiwan Series (*N*=35)	0	2 (5.7)

European Journal of Haematology 86 (16–22)

ORIGINAL ARTICLE

Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group

Meral Beksac[1], Rauf Haznedar[2], Tulin Firatli-Tuglular[3], Hakan Ozdogu[4], Ismet Aydogdu[5], Nahide Konuk[1], Gulsan Sucak[2], Işık Kaygusuz[3], Sema Karakus[4], Emin Kaya[6], Ridvan Ali[7], Zafer Gulbas[8], Gulsum Ozet[9], Hakan Goker[10], Levent Undar[11]

Table 4 Frequency of grade 3–4 toxicities observed in each treatment arm after 8 cycles of treatment

	Melphalan–prednisone–thalidomide		Melphalan–prednisone		
	n	%	*n*	%	*P*-value
Hematologic AEs	14	24.6	8	14.3	0.168
Infection	13	22.4	4	7.0	0.033
Neuropathy	5	8.6	2	3.5	0.438
Constipation	3	5.2	2	3.5	1.000
Pulmonary embolism	3	5.2	0	0.0	0.243
Skin reactions	2	3.4	1	1.8	1.000
Venous thrombosis	1	1.7	3	5.3	0.364
Cardiac AEs	1	1.7	5	8.8	0.114

Table 5 Anticoagulation prophylaxis given in each arm

	Melphalan–prednisone–thalidomide ($n = 58$)		Melphalan–prednisone ($n = 57$)	
	n	%	*n*	%
Low-dose ASA	19	32.8	10	17.5
LMWH	20	34.5	4	7.0
Low-dose WAR	4	6.9	2	3.5
Full-dose WAR	3	5.2	0	0
High-dose ASA	1	1.7	0	0
None	11	19.0	41	71.9

Low-dose ASA, aspirin 100 mg/d; LMWH, low molecular weight heparin; low-dose WAR, warfarin 2.5–5 mg/d; full-dose WAR; warfarin adjusted according to INR = 2–2.5; high-dose ASA, 300–500 mg/d aspirin.

Family history of venous thromboembolism is associated with increased risk for thrombosis in multiple myeloma: a population-based study

Table 1 Venous thromboembolism (VTE) among multiple myeloma patients and matched controls, and family history

Variable	Multiple myeloma patients (N = 21 067)	Matched controls (N = 83 094)
VTE	1429	4986
With family history	122	316
Without family history	1307	4670
Risk of VTE by family history, OR (95% CI)	2.2 (1.8–2.7)*	1.5 (1.3–1.7)*

*The risk of VTE was significantly higher (P = 0.002) in multiple myeloma patients with a family history of VTE than in controls with a family history of VTE.

İsveç

1964-2004

>20.000 hasta
83.000 kontrol

J Thromb Haemost 2012;10:962-4

Tedavi İlişkili Risk Faktörleri

Yüksek doz dexamethasone (≥ 480 mg/ay)

Aynı anda Eritropoetin kullanımı

IMID ler (Thalidomide, Lenalidomide, Pomalidomide)

IMID ler ile yüksek doz dexamethasone veya

IMID ler + Doxorubicin veya

IMID+ Çoklu kemoterapi

Table 3 Overall Indirect Comparison of Rates of DVT/PE Reported With TD and VTD, MPT and VMPT, and RD/Rd and RVD

Regimen	Study	n	DVT/PE Rate, % (grade 3/4 unless specified)	Prophylaxis
TD	Rajkumar et al, 2006[76]	102	20	None per protocol
	Rajkumar et al, 2008[22]	235	18.8	34% received aspirin
	Ludwig et al, 2009[70]	134	15	LMWH recommended for 6 months after first 48 patients.
	Macro et al, 2006[71]	100	22.8	Not systematically given
	Cavo et al, 2010[52]	238	5	LMWH/low-dose warfarin/aspirin
	Rosiñol et al, 2009[62]	104	8	Not specified
	Gay et al, 2010[66]	183	15.3	Not specified

%5-22

Clinical Lymphoma Myeloma&Leukemia 2011;11(2):228-36

Table 3 Overall Indirect Comparison of Rates of DVT/PE Reported With TD and VTD, MPT and VMPT, and RD/Rd and RVD

Regimen	Study	n	DVT/PE Rate, % (grade 3/4 unless specified)	Prophylaxis
VTD	Cavo et al, 2010[52]	236	3	LMWH/low-dose warfarin/aspirin
	Rosiñol et al, 2009[62]	102	1	Not specified
	Moreau et al, 2010[59]	100	1	LMWH
	Niesvizky et al, 2010[60]	93	5[a]	Aspirin, LMWH, or full-dose warfarin

%1-5

Clinical Lymphoma Myeloma&Leukemia 2011;11(2):228-36

Table 3 Overall Indirect Comparison of Rates of DVT/PE Reported With TD and VTD, MPT and VMPT, and RD/Rd and RVD

Regimen	Study	n	DVT/PE Rate, % (grade 3/4 unless specified)	Prophylaxis
MPT	Palumbo et al, 2006, 2008[72,74]	167	11[b]	Enoxaparin 40 mg/day for 4 cycles after first 65 patients
	Facon et al, 2007[65]	125	12	No systemic prophylaxis prospectively planned
	Hulin et al, 2010[67]	113	6	No anticoagulation prophylaxis prospectively planned
	Waage et al, 2010[78]	182	8	None recommended; 40% of patients taking drugs with potential prophylactic effect
	Wijermans et al, 2010[79]	165	10[c]	LMWH recommended from 2005
VMPT	Boccadoro et al, 2010[51]	254	5	LMWH/low-dose warfarin/aspirin

%5-12

Clinical Lymphoma Myeloma&Leukemia 2011;11(2):228-36

Table 3 Overall Indirect Comparison of Rates of DVT/PE Reported With TD and VTD, MPT and VMPT, and RD/Rd and RVD

Regimen	Study	n	DVT/PE Rate, % (grade 3/4 unless specified)	Prophylaxis
RD	Rajkumar et al, 2010[77]	223	26	Recommended, then mandated for approximately half of patients
	Zonder et al, 2010[80]	97	23.5	Aspirin 325 mg/day after first 21 patients
Rd	Rajkumar et al, 2010[77]	222	12	Recommended, then mandated for approximately half of patients
	Palumbo et al, 2010[81]	370	2[d]	Aspirin or LMWH
RD/Rd	Gay et al, 2010[66]	228	9.2	Not specified
RVD/d	Richardson et al, 2010[61]	66	6[e]	Aspirin or alternative anticoagulation

%2-26

Clinical Lymphoma Myeloma&Leukemia 2011;11(2):228-36

Relapse/refrakter Myeloma

MM-10 R+Dex 11.4% vs 4.6% plasebo+Dex
Profilaktik antikoagülasyon önerisi çalışmada yoktu

N Engl J Med 2007;357:2123-32

MM-09 R+Dex vs plasebo+Dex 14.7% vs 3.4%

N Engl J Med 2007; 357:2133-2142

Table 2 VTE rates in patients with multiple myeloma treated with thalidomide or lenalidomide and dexamethasone

Study	*N*	Therapy	Prophylaxis	VTE rate (%)
Dimopoulos et al. [11]	351	Len/high dose Dex vs. Placebo/Dex	None	11.4 vs. 4.6
Weber et. al [8]	353	Len/high dose Dex vs. Placebo/Dex	None	14.7 vs. 3.4
Zonder et al. [12]	198	Len/high dose Dex vs. high dose Dex	ASA (not initially)	12.6 vs. 3.5
Rajkumar et al. [14]	445	Len/high dose Dex vs. Len/Dex low dose	ASA	25 vs. 9
Palumbo et al. [16]	200 (interim analysis)	Thal-based therapy	ASA vs. LMWH vs. low-fixed dose warfarin	9 3 3
Minnema et al. [24]	211	Thal/Adriamycin/Dex high dose (TAD)	LMWH	8
Klein et al. (this study)	45	Len/intermediate Dex	LMWH	2.2

Ann Hematol 2009;88:67-71

Lit-17

healthcare

MDPI

Artide

Impact of Time-Varying Treatment Exposures on the Risk of Venous Thromboembolism in Multiple Myeloma

Joshua D. Brown [1,2,*], Val R. Adams [1] and Daniela C. Moga [1]

1 Department of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Lexington, KY 40536, USA; val.adams@uky.edu (V.R.A.); daniela.moga@uky.edu (D.C.M.)

2 Department of Pharmaceutical Outcomes & Policy, University of Florida College of Pharmacy, Gainesville, FL 32610, USA

* Correspondence: josh.brown@uky.edu; Tel.: +1-859-218-0229

Academic Editor: Sampath Parthasarathy

Received: 12 October 2016; Accepted: 14 December 2016; Published: 20 December 2016

13.700 hastanın 1 yıl boyunca takibinde
1050 trombotik olay oldu.
756 DVT (%72), 294 PE (%28).

Olayların neredeyse yarısı teşhisten sonraki ilk 90 günde oldu.

Healthcare 2016, 4, 93; doi:10.3390/healthcare4040093

Lit-17

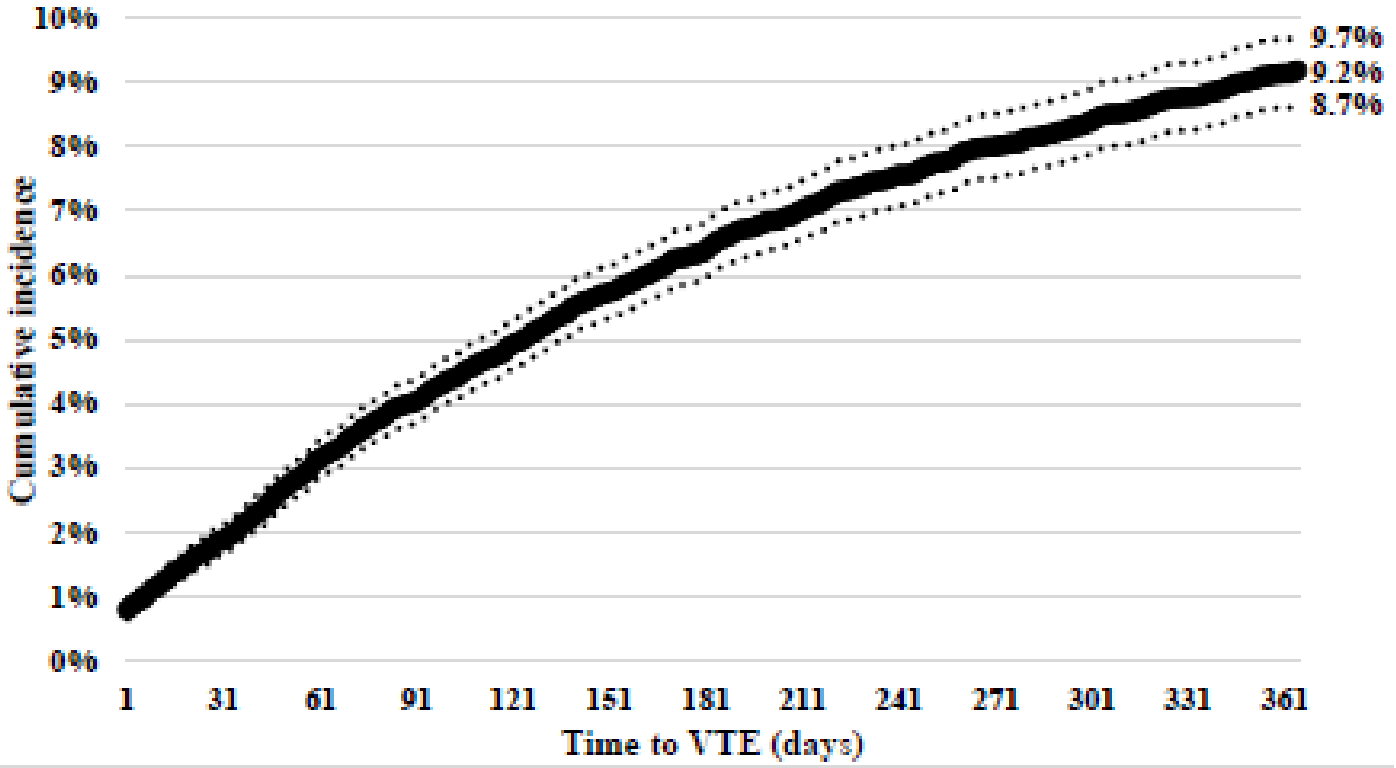


Figure 1. Cumulative incidence and 95% confidence interval of venous thromboembolism (VTE) from diagnosis of multiple myeloma.

Healthcare 2016, 4, 93; doi:10.3390/healthcare4040093

1050 Tromboz
13,700 kişi/ 1 yıl

VTE’lerin yarısı ilk 90 gün içinde

- Yaş
- Kalp yetmezliği
- Hipertansiyon

IMID’lerin etkisi önceki literatürlere göre daha düşük bulundu

Lit-17

Healthcare **2016**, *4*, 93; doi:10.3390/healthcare4040093

Time-Varying Exposures	HR	95% CI	
	Overall		
Thalidomide derivatives	1.38	1.06	1.79
Proteasome Inhibitors	0.80	0.51	1.26
Steroids	1.54	1.21	1.96
Cytotoxic chemotherapy	1.15	0.76	1.73
Infections	2.29	1.80	2.92
Erythropoiesis-stimulating agents	1.03	0.64	1.67
Colony stimulating factors	0.93	0.43	1.99
Stem cell transplant	2.40	0.99	5.83
Central venous catheters	2.02	1.65	2.49
Hospitalization	8.90	7.26	10.92

Lit-17

Healthcare 2016, *4*, 93; doi:10.3390/healthcare4040093

Bortezomib

proteasome inhibitor bortezomib ile tedavi,

Artmış VTE riski ile ilişkili bulunmadı (<%2)

Low VTE Risk With Bortezomib in Multiple Myeloma

Table 1 Rates of DVT and PE in the VMP and MP Arms in the Phase 3 VISTA Trial in Previously Untreated MM,[37] and in the Single-agent Bortezomib and Dexamethasone Arms in the Phase 3 APEX Trial in Relapsed MM According to Erythropoietin Use[39]

VISTA (Richardson et al, 2009[37])	VMP, n = 340[a]		MP, n = 337[a]	
DVT, n (%)	5 (1)		6 (2)	
Grade 3/4, n (%)	4 (1)/0		2 (<1)/0	
PE, n (%)	4 (1)		3 (1)	
Grade 3/4, n (%)	0/2 (<1)		1 (<1)/2 (<1)	
DVT/PE, n (%)	7 (2)		7 (2)	
APEX (Lonial et al, 2008[39])	**Bortezomib**		**Dexamethasone**	
	EPO (n = 137)	**No EPO (n = 194)**	**EPO (n = 106)**	**No EPO (n = 226)**
DVT, n (%)	1 (0.7)	0	2 (1.9)	4 (1.8)
PE, n (%)	1 (0.7)	0	1 (0.9)	4 (1.8)
DVT/PE, n (%)	2 (1.5)	0	3 (2.8)	6 (2.7)

Clinical Lymphoma Myeloma&Leukemia 2011;11(2):228-36

Low VTE Risk With Bortezomib in Multiple Myeloma

Table 2 Direct Comparisons of DVT/PE Rates Between Regimens of Thrombogenic Potential With or Without Bortezomib (comparisons between 2 or more arms within the same study or between 2 regimens investigated according to the same study design at the same center)

	Study	Regimen	n	DVT/PE Rate, %	Prophylaxis	*P* Value
Zangari et al[82]	UARK 2001-12	DT-PACE	98	10	Anticoagulation prophylaxis	.0006
	UARK 2003-33	VDT-PACE	69	0		
Palumbo et al[83]	GIMEMA phase 3 prophylaxis study	TD[a]	240	7.2	Aspirin 100 mg/day, warfarin 1.25 mg/day, or enoxaparin 40 mg/day	.09 (no bortezomib vs. bortezomib-containing regimen)
		VTD	236	5.1		
		VMPT	191	4.8		
Cavo et al[52]	GIMEMA phase 3 trial	TD[a]	238	5	Aspirin 100 mg/day, warfarin 1.25 mg/day, or enoxaparin 40 mg/day	.53
		VTD	236	3		
Rosinol et al[62]	GEM05MENOS65 phase 3 trial	TD	104	8	None	.01
		VTD	102	1		

Clinical Lymphoma Myeloma&Leukemia 2011;11(2):228-36

Arteriyel Trombotik Komplikasyonlar

Table 3. Multivariate Analysis of Risk Factors Associated with Stroke.

	Unadjusted		Adjusted		*P* value
	Odds Ratio	95% CI	Odds Ratio	95% CI	
Smoking	2.35	1.03–5.36	2.324	0.98–5.54	0.0572
Nephropathy	3.63	1.45–9.07	3.528	1.36–9.14	0.0094
MM Stage I and II	2.53	1.24–5.17	2.77	1.31–5.81	0.0073

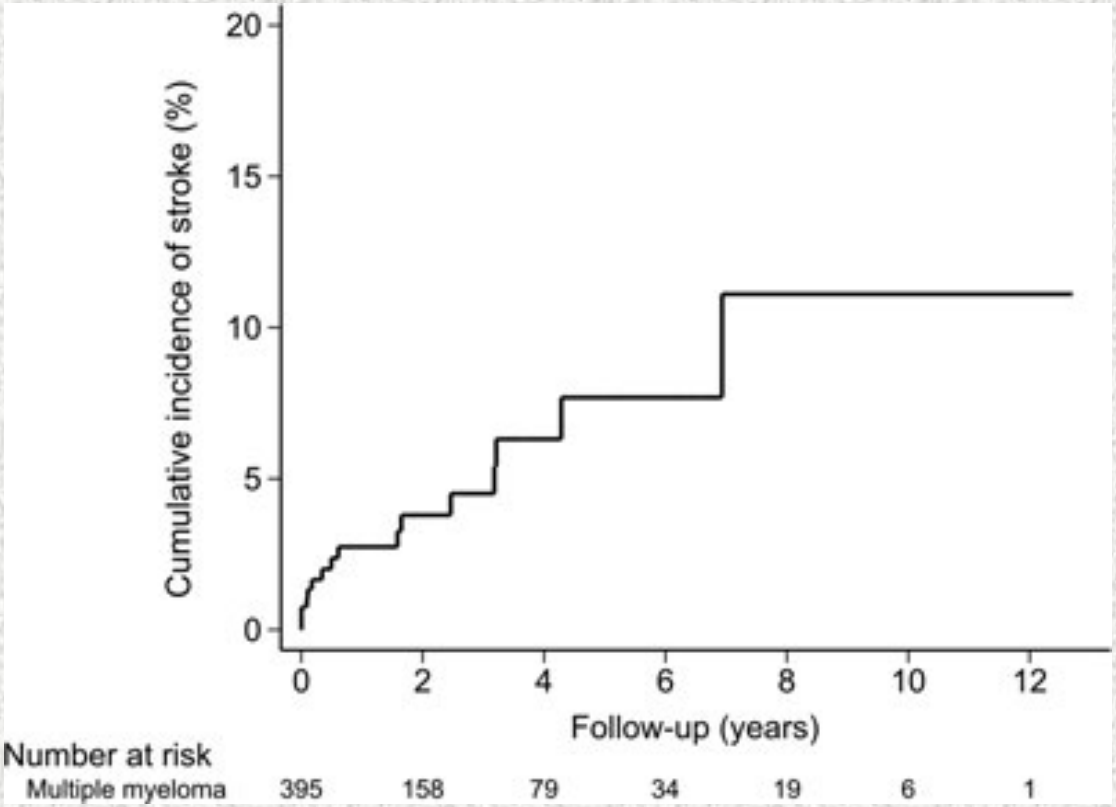
doi:10.1371/journal.pone.0166627.t003

Renal yetmezlik,

Evre I ve II, stroke için bağımsız risk faktörleri

Lit-19

1148 hasta
46 vasküler olay



Yeni tanı MM hastalarında stroke riski

5-yıllık ‘estimated cumulative incidence’ %7.45

Hematological Oncology 2017;726-733

İnme riski

Serum kreatinin > 2mg/dL

κ hafif zincir

Daha önceki serebrovasküler olaylar

Lit-22

Hematological Oncology 2017;726-733

Early Thrombosis of Arteriovenous Fistula

Table 1 Baseline patient characteristics and incidence of early thrombosis within 30 d after surgical creation of a radiocephalic arteriovenous fistula

		Total (n)	Early thrombosis (n, %)	P
Sex	Female	24	5 (20.8)	0.316
	Male	67	8 (11.9)	
Age	≥65 y	50	6 (12.0)	0.556
	<65 y	41	7 (17.0)	
Race	Non-white	91	13 (14.2)	–
	White	0	–	
Diabetes mellitus	Yes	43	7 (16.2)	0.766
	No	48	6 (12.5)	
Coronary artery disease	Yes	12	1 (8.3)	1.000
	No	79	12 (15.2)	
Peripheral vascular disease	Yes	6	2 (33.3)	0.203
	No	85	11 (12.9)	
Plasma cell neoplasm	Yes	8	4 (50.0)	0.013*
	No	83	9 (10.8)	

Multiple Myeloma n: 5
AL Amyloidosis n: 3

Hemodialysis International 2018;22:176-179

lit-13

Table 2 Risk factors for early thrombosis within 30 d after surgical creation of a radiocephalic arteriovenous fistula

	Adjusted OR (95% CI)	P
Female sex (vs. male)	4.1 (0.9–19.0)	0.070
Age ≥65 y (vs. <65 y)	0.5 (0.1–2.0)	0.332
Diabetes mellitus	3.7 (0.6–22.3)	0.150
Coronary artery disease	0.7 (0.1–6.9)	0.747
Peripheral vascular disease	4.5 (0.6–34.9)	0.150
Plasma cell neoplasm	38.8 (4.0–378.9)	0.002*

lit-13

Hemodialysis International 2018;22:176-179

SURVEY-Swedish Cancer Registry

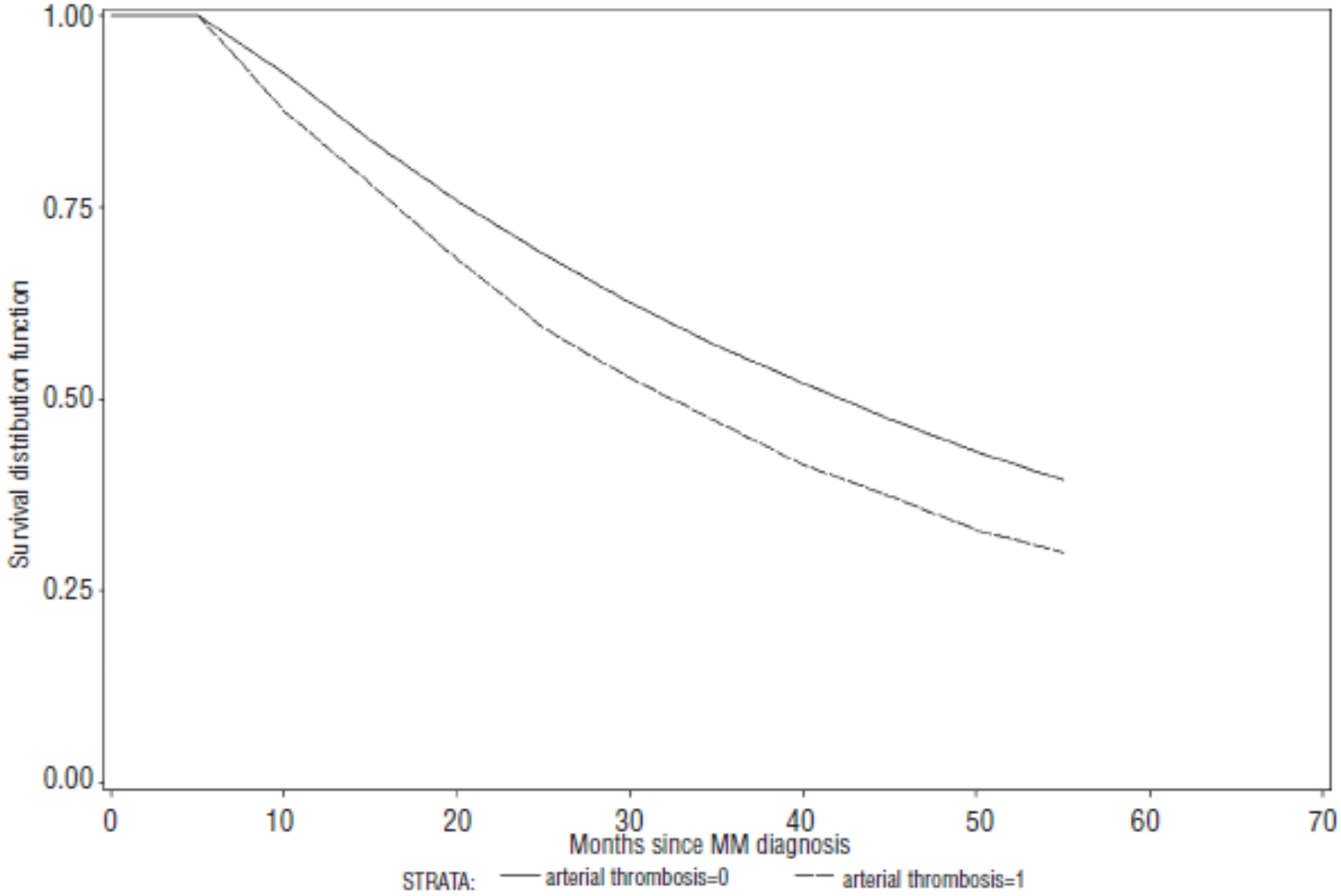
Table 1. Risk of death among multiple myeloma patients with thrombosis compared to those without.

	HR for death within 1 year of MM diagnosis (95% CI)	HR for death within 5 years of MM diagnosis (95% CI)	HR for death within 10 years of MM diagnosis (95% CI)
Any thrombosis	3.4 (3.0-3.8)	2.1 (2.0-2.2)	2.0 (1.9-2.2)
Any venous thrombosis	2.9 (2.4-3.5)	1.6 (1.5-1.8)	1.6 (1.4-1.7)
DVT only	1.9 (1.4-2.5)	1.4 (1.2-1.6)	1.4 (1.2-1.6)
PE only	4.7 (3.7-6.0)	2.1 (1.8-2.5)	1.9 (1.6-2.2)
Any arterial thrombosis	3.4 (3.0-3.8)	2.2 (2.0-2.3)	2.1 (1.9-2.1)
MI/angina only	3.0 (2.6-3.4)	2.0 (1.9-2.2)	2.0 (1.8-2.1)
Stroke/TIA only	4.1 (3.3-5.1)	2.3 (2.0-2.6)	2.1 (1.9-2.4)
Before 2000			
Any arterial thrombosis	3.4 (3.0-3.9)	2.3 (2.1-2.5)	2.2 (2.0-2.3)
Any venous thrombosis	3.1 (2.5-3.8)	1.7 (1.5-1.9)	1.6 (1.5-1.8)
After 2000			NA
Any arterial thrombosis	3.6 (2.7-4.9)	2.7 (2.1-3.4)	NA
Any venous thrombosis	1.9 (1.0-3.5)	1.6 (1.1-2.5)	NA

9399 hasta
1987-2006

lit-2

Haematologica 2012;97(10):1603-1607



Haematologica 2012;97(10):1603-1607 lit-2

Myelom teşhisinin ilk 6 ayında

Arteriyel tromboz geçirmek,

mortaliteyi 1., 5. ve 10. yıllarda

geçirmeyenlere göre belirgin arttırmıştır

Haematologica 2012;97(10):1603-1607

lit-2

Miyelom İlişkili Faktörler

- Hastalığın durumu
- Hipervizkozite

MGUS

Table II. Multivariate analysis of risk factors for thrombosis in the follow-up cohort of 1238 patients with monoclonal gammopathy of undetermined significance.

	Arterial thrombosis Hazard ratio (95% CI)	Venous thrombosis Hazard ratio (95% CI)
Male gender	1·15 (0·46–2·85)	1·02 (0·75–1·39)
Age >60 years	2·85 (0·97–8·33)	1·04 (0·47–2·29)
Remote thrombosis	No patient	4·14 (0·90–18·87)
Cardiovascular risk factors	4·92 (1·42–17·04)	0·50 (0·16–1·52)
M-protein >16 g/l	1·22 (0·49–3·02)	3·08 (1·01–9·36)
Bidonal gammopathy	No patient	6·21 (0·78–49·12)

British Journal of Haematology 2013;160:673-79

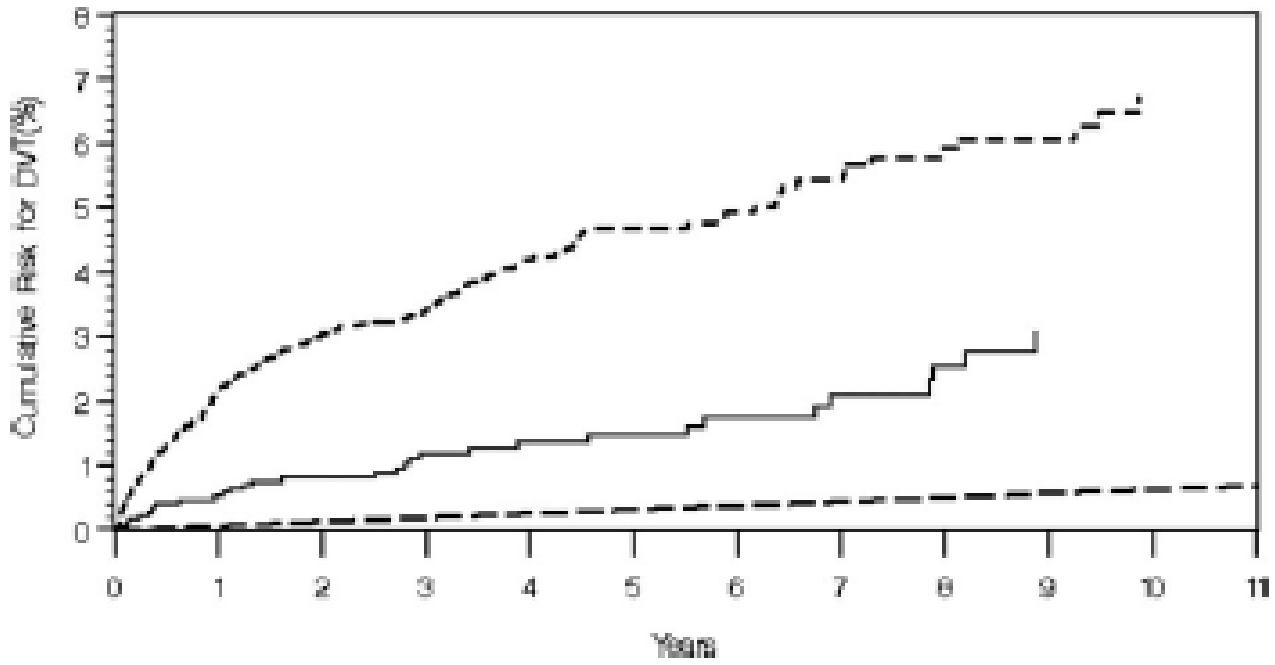


Figure 2. Cumulative risk of DVT among 2374 MGUS cases (solid line), 6192 patients with multiple myeloma (short dashed line), and 4 187 631 persons without a diagnosis of MGUS/multiple myeloma (long dashed line).

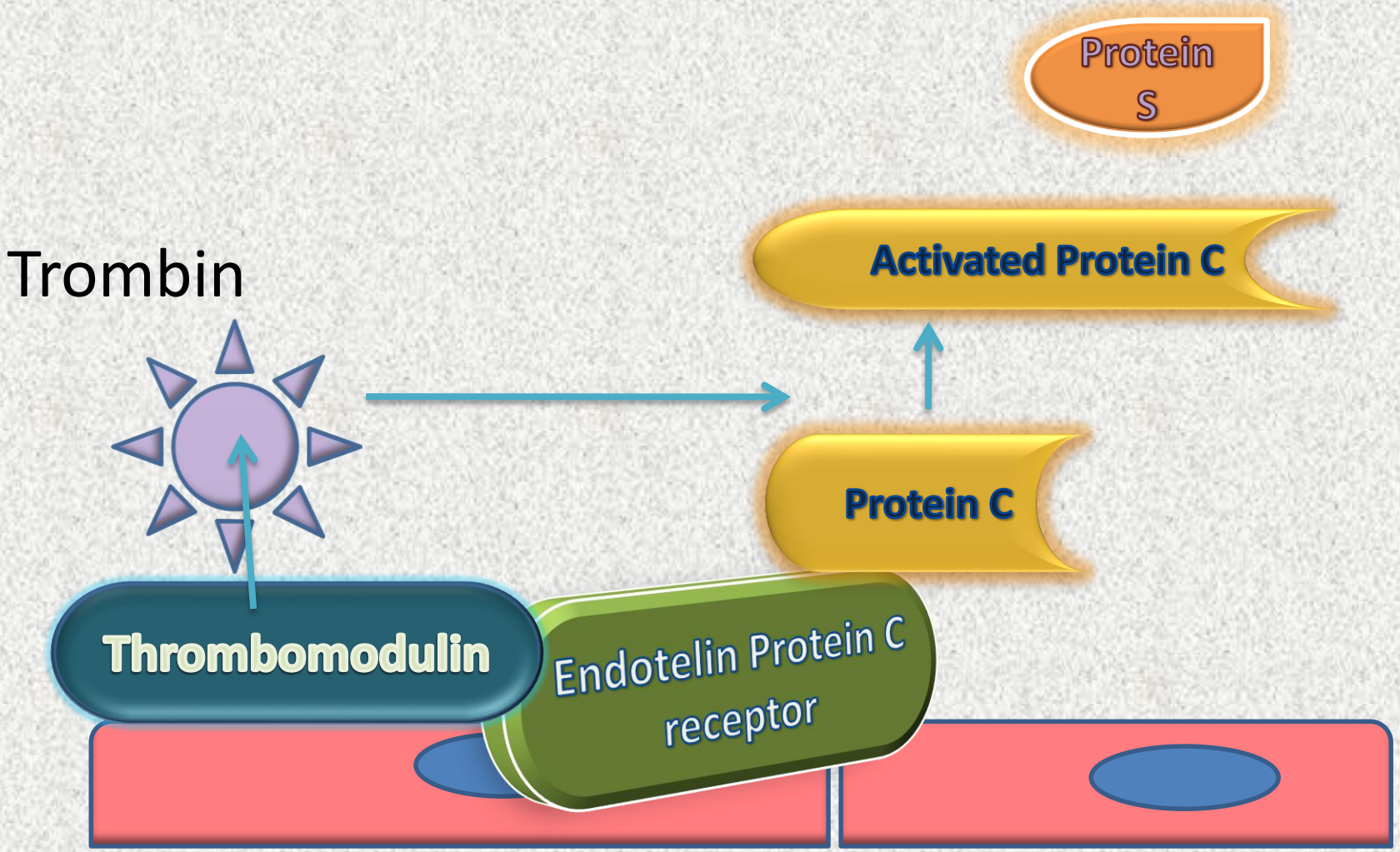
Blood 2008;112: 3582-86

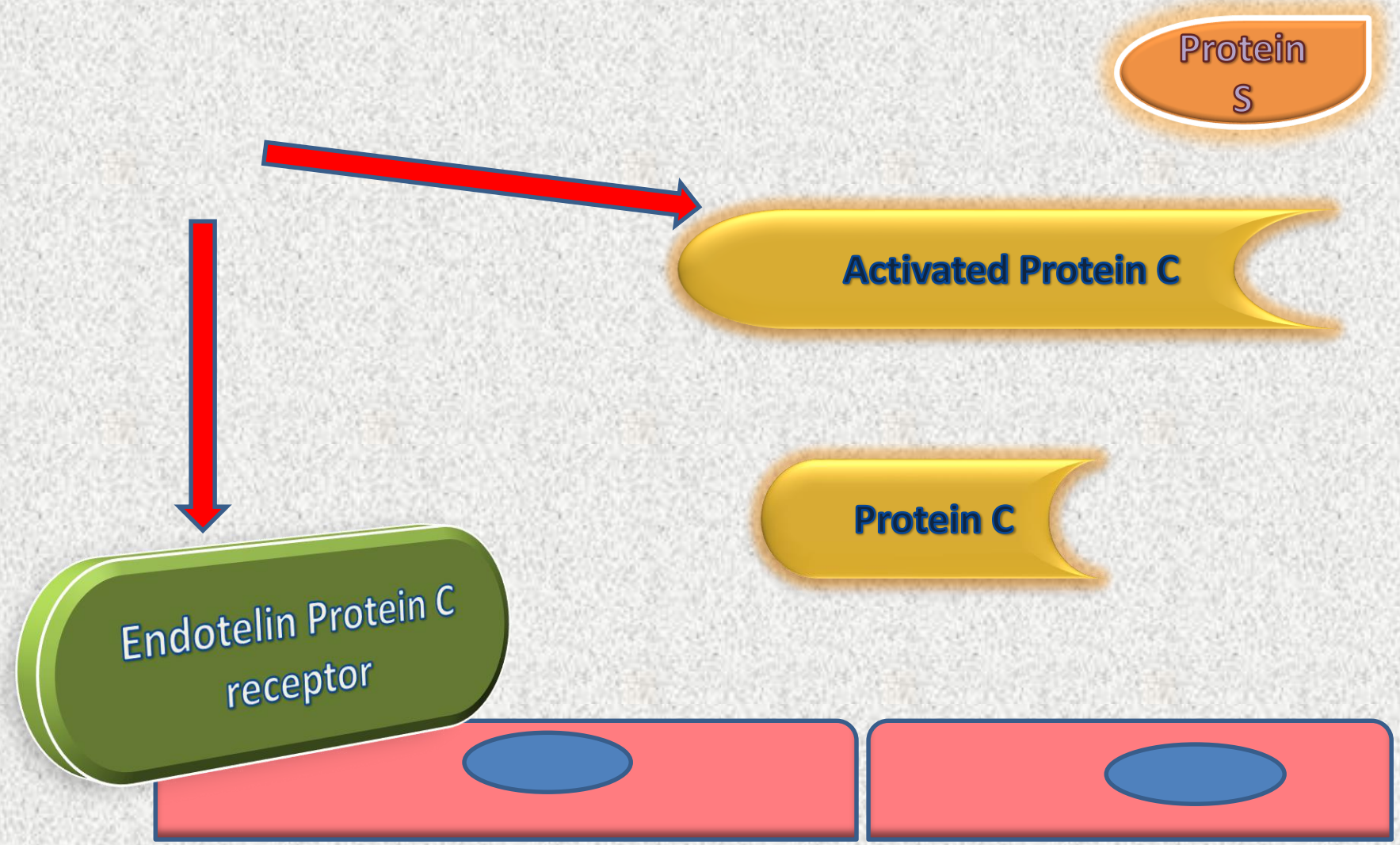
Teşhis ve DVT riski……MGUS 3.3
MM 9.2

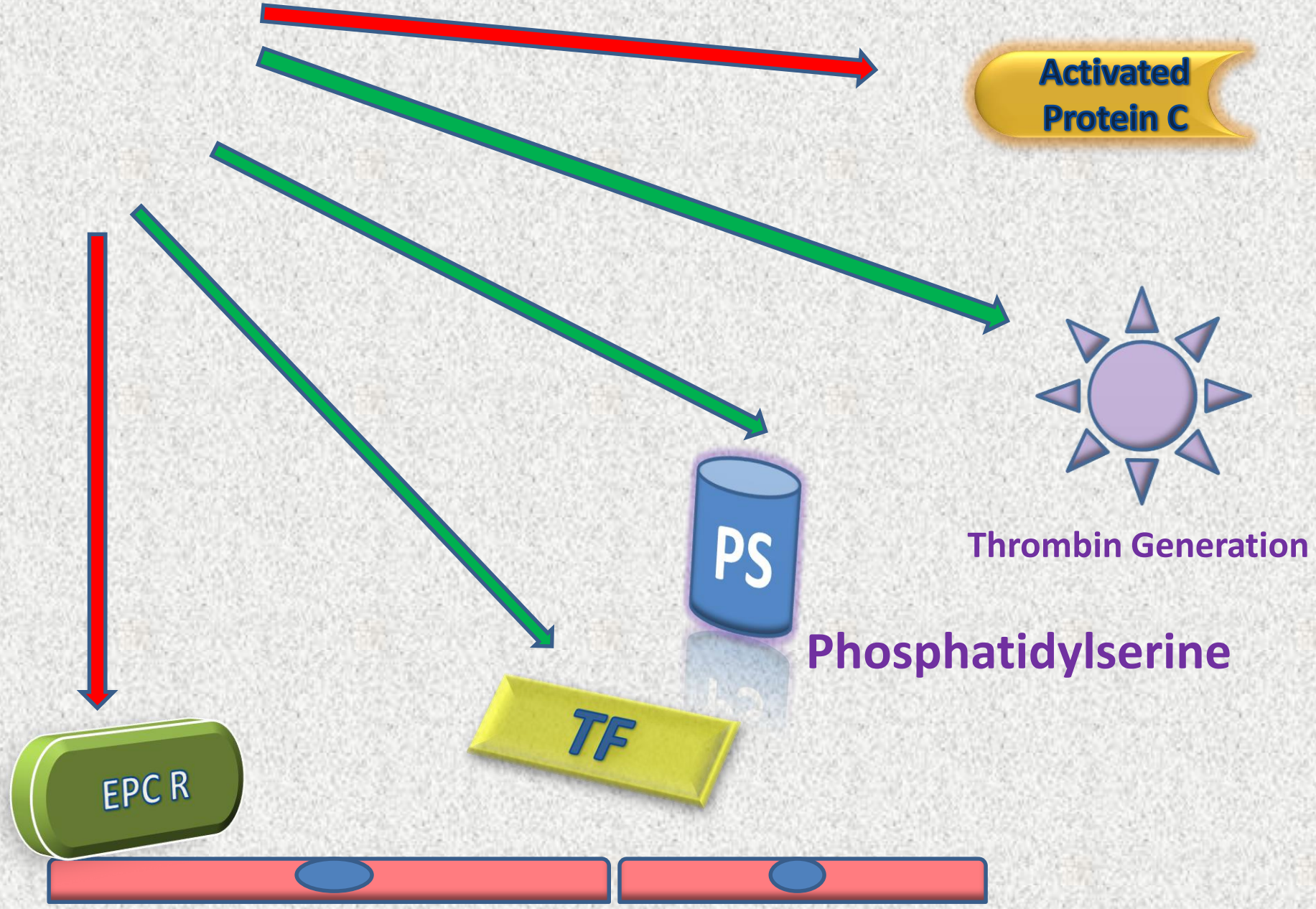
İlk yıl için DVT riski……MGUS 8.4
MM 11.6

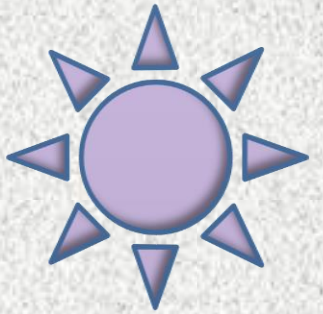
Blood 2008;112: 3582-86

Hemostatik Anormallikler


Protein S
Trombin
Activated Protein C
Protein C
Thrombomodulin
Endotelin Protein C receptor

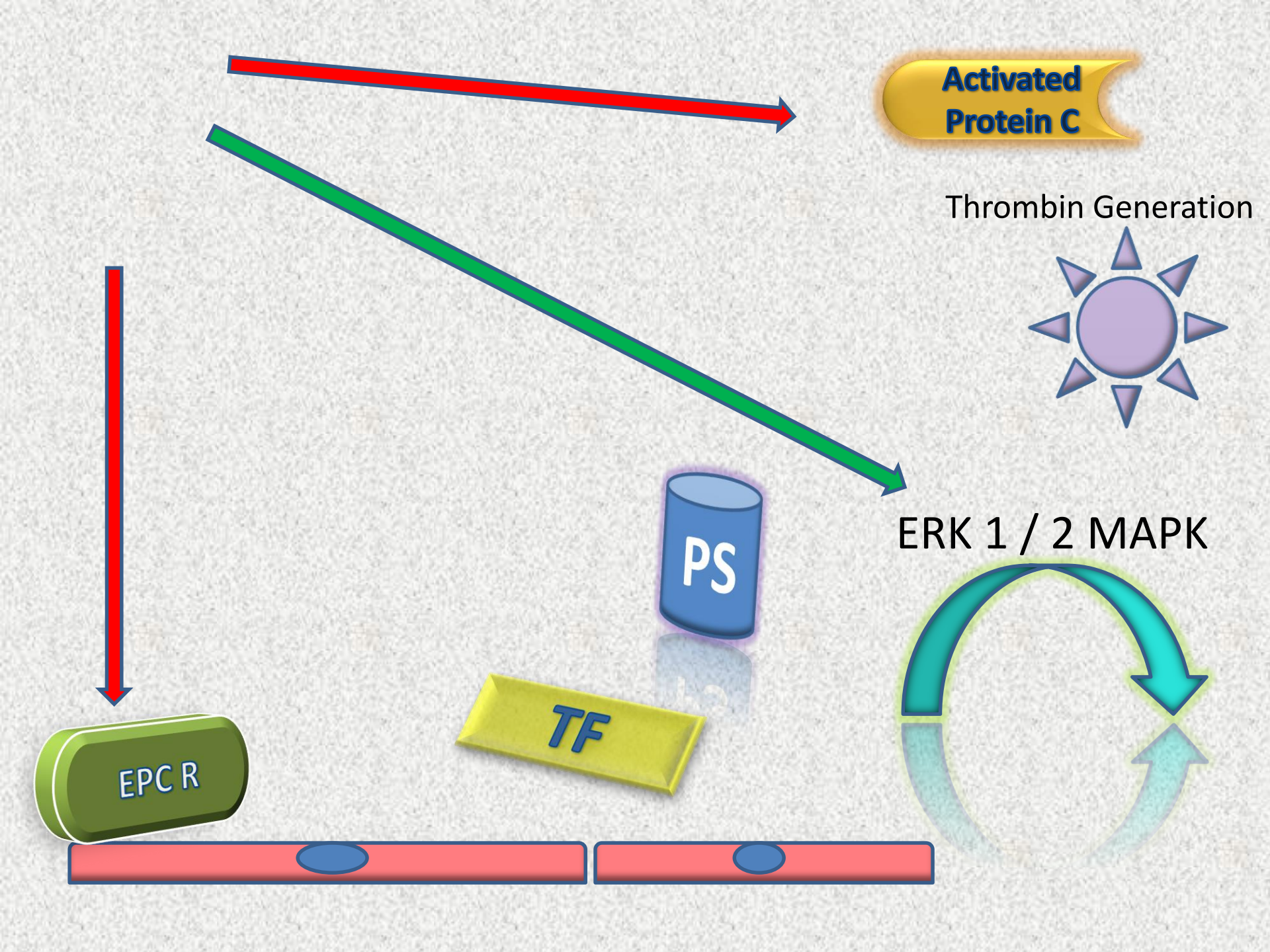

Protein S
Activated Protein C
Protein C
Endotelin Protein C receptor

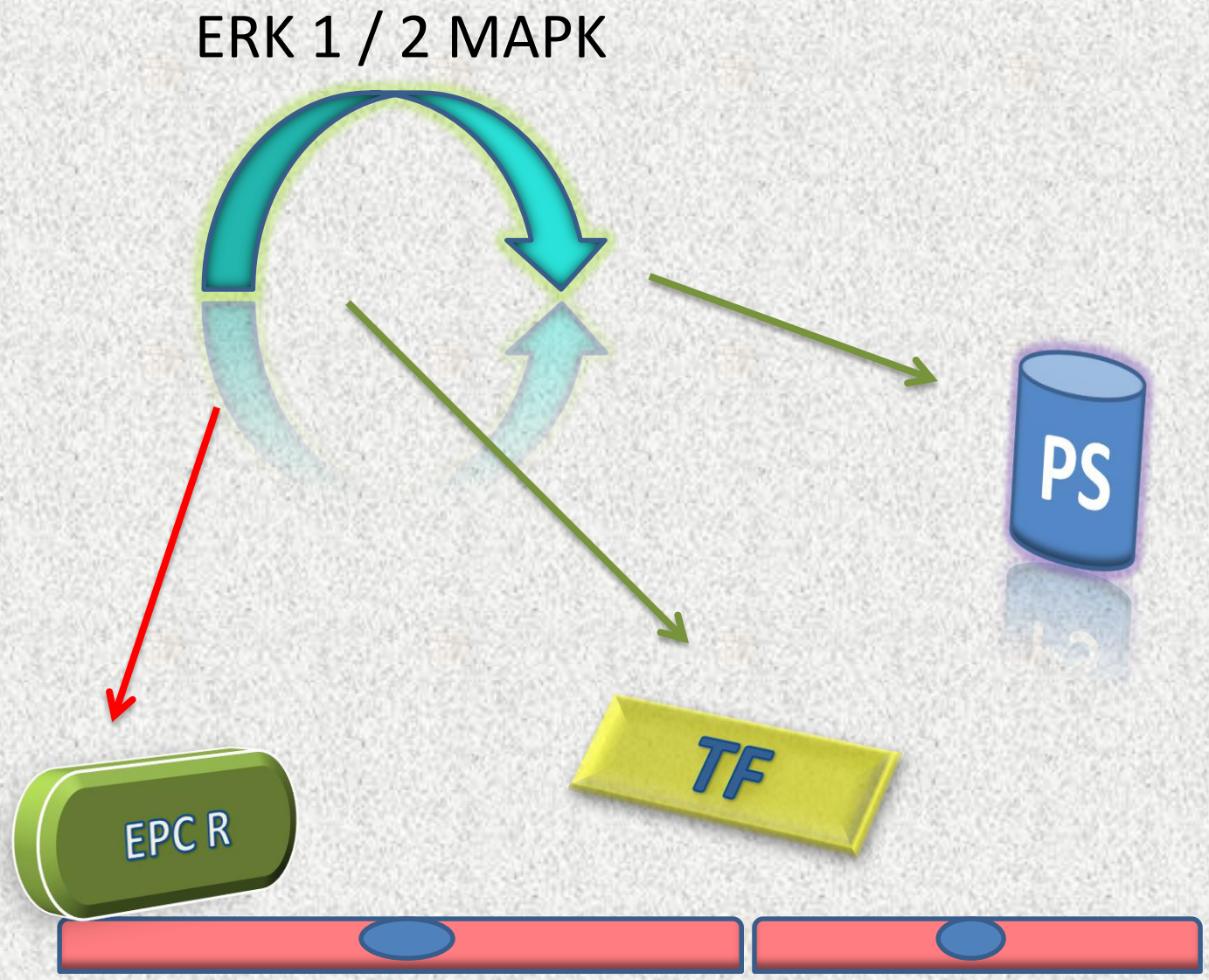

Activated
Protein C
PS
Thrombin Generation
Phosphatidylserine
TF
EPC R



Thrombin Generation

Extrinsic Coagulation Cascade


Activated Protein C
Thrombin Generation
ERK 1 / 2 MAPK
PS
TF
EPC R

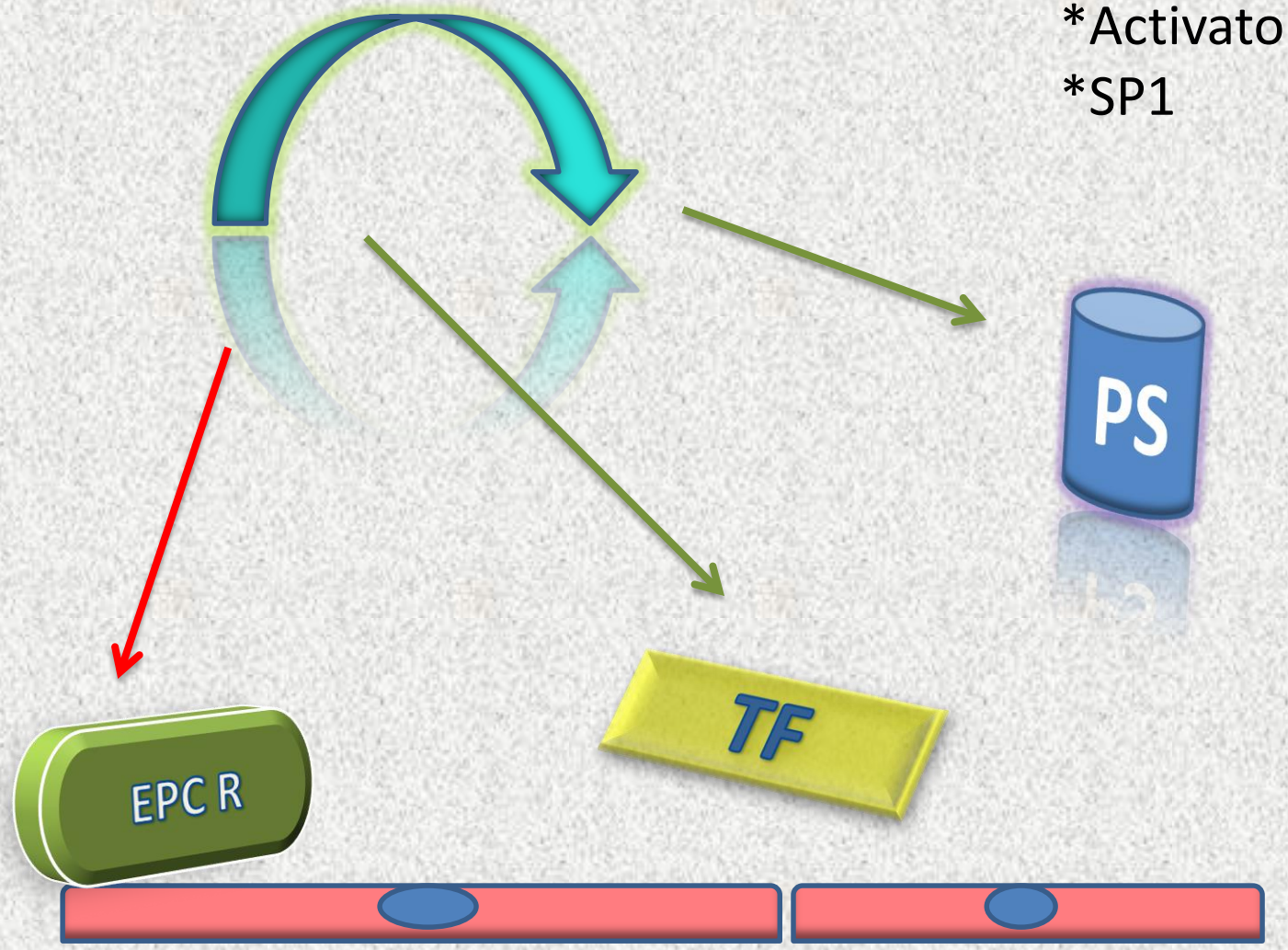


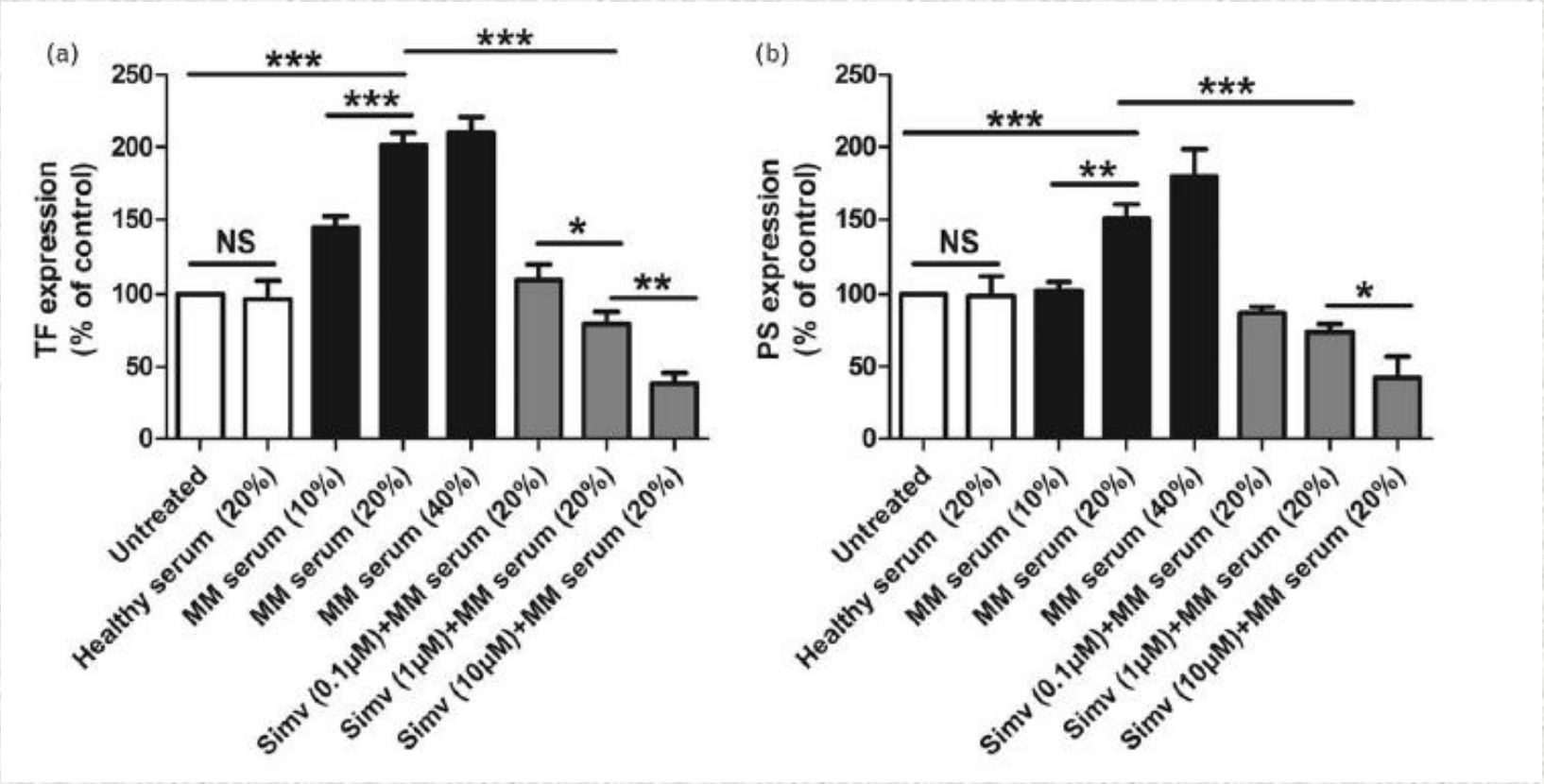
lit-4

Other Pathways

*Nuclear Factor Kappa β
*Activator protein-1
*SP1

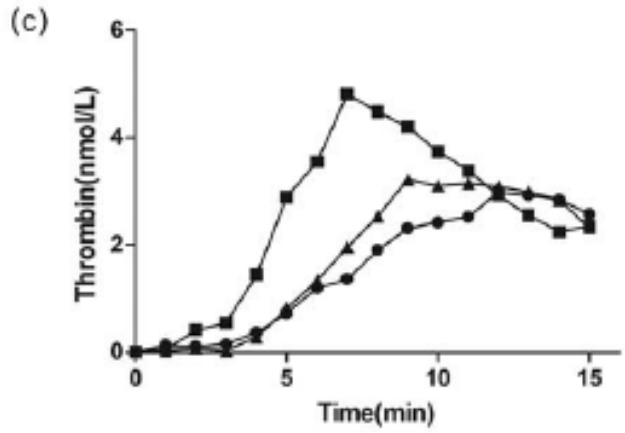
ERK 1 / 2 MAPK

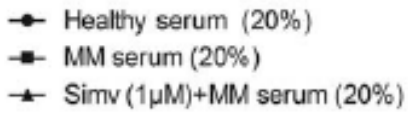


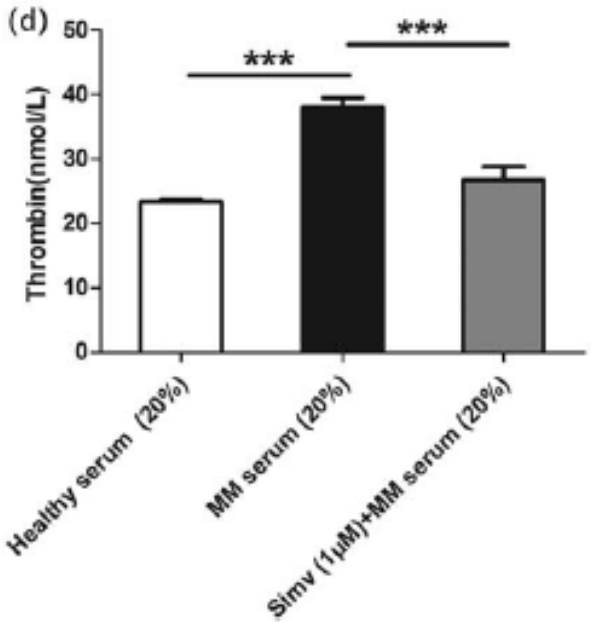


Human umbilical vein endothelial cells (HUVECs)

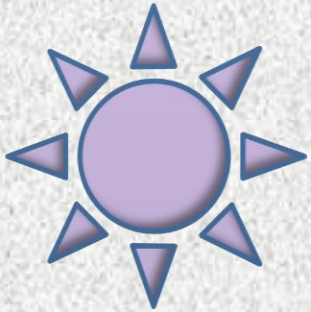
Blood Coagulation and Fibrinolysis 2018, 29:00–00





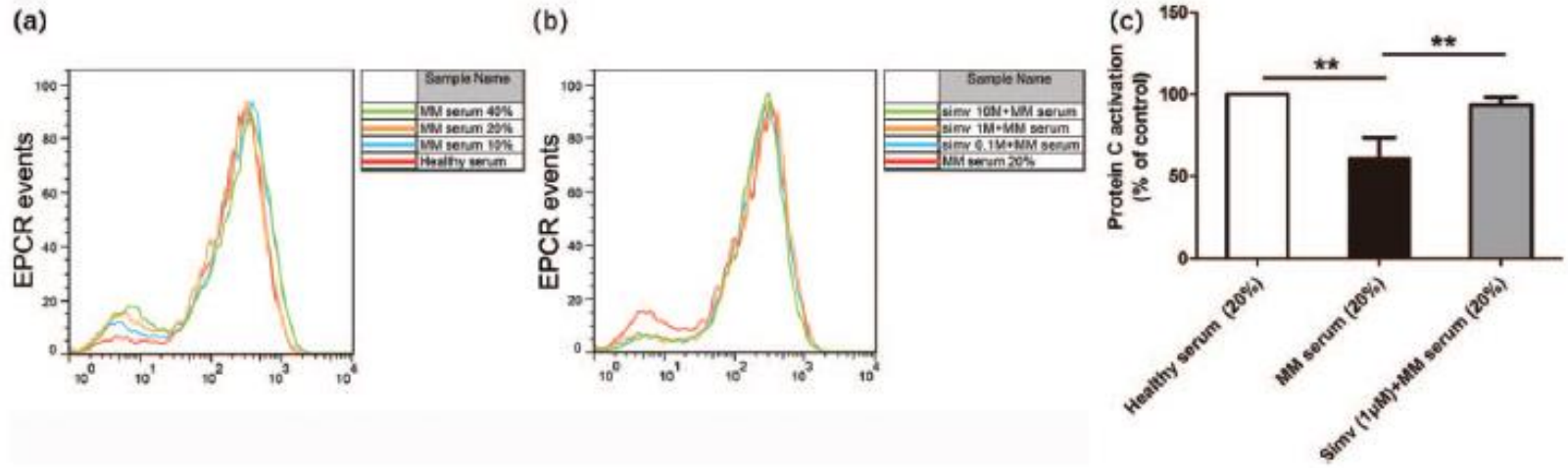


Blood Coagulation and Fibrinolysis 2018, 29:00–00



Thrombin Generation

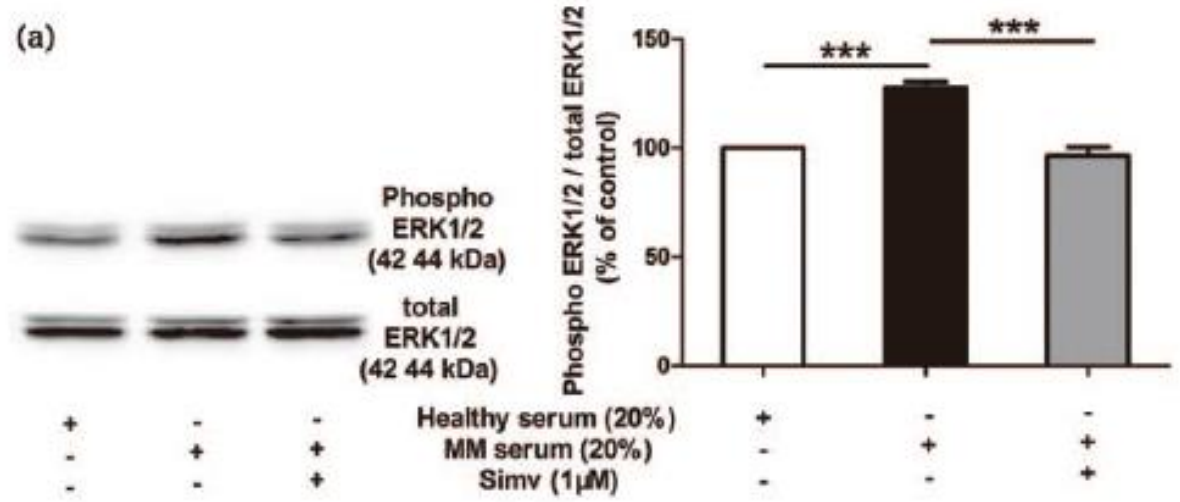
Fig. 2



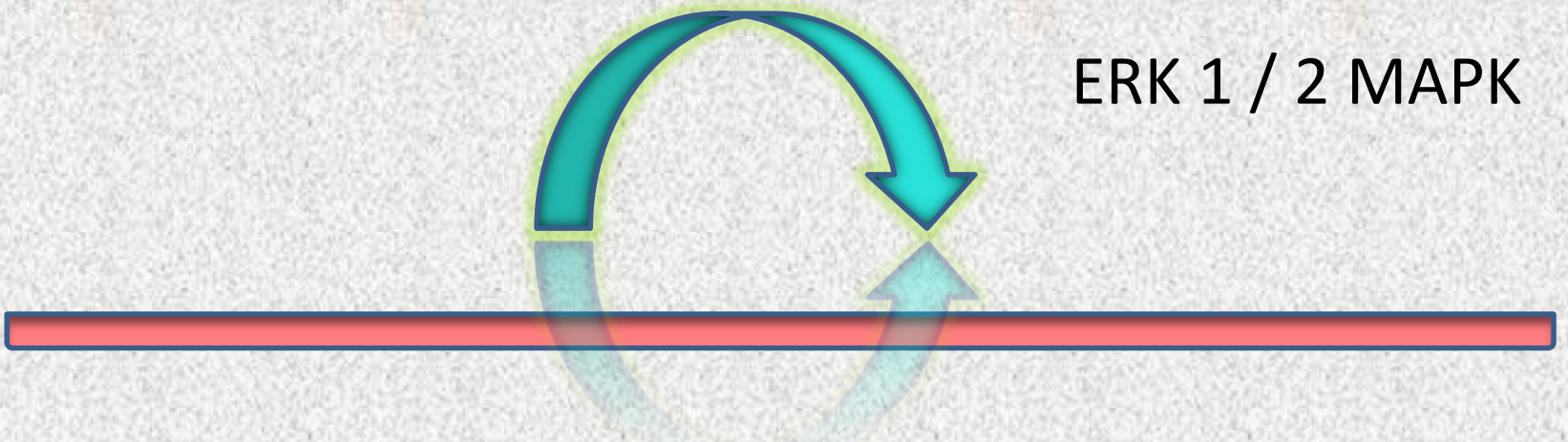
Blood Coagulation and Fibrinolysis 2018, **29**:00–00

EPC R

Fig. 3



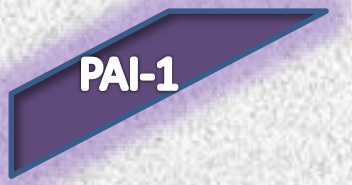
Blood Coagulation and Fibrinolysis 2018, 29:00–00



ERK 1 / 2 MAPK

Thrombosis-related Biomarkers

PDMP (Platelet-derived microparticles)



PAI-1 (Plasminogen activator inhibitor-1)

HMGB1 (High Mobility Group Box Protein-1)

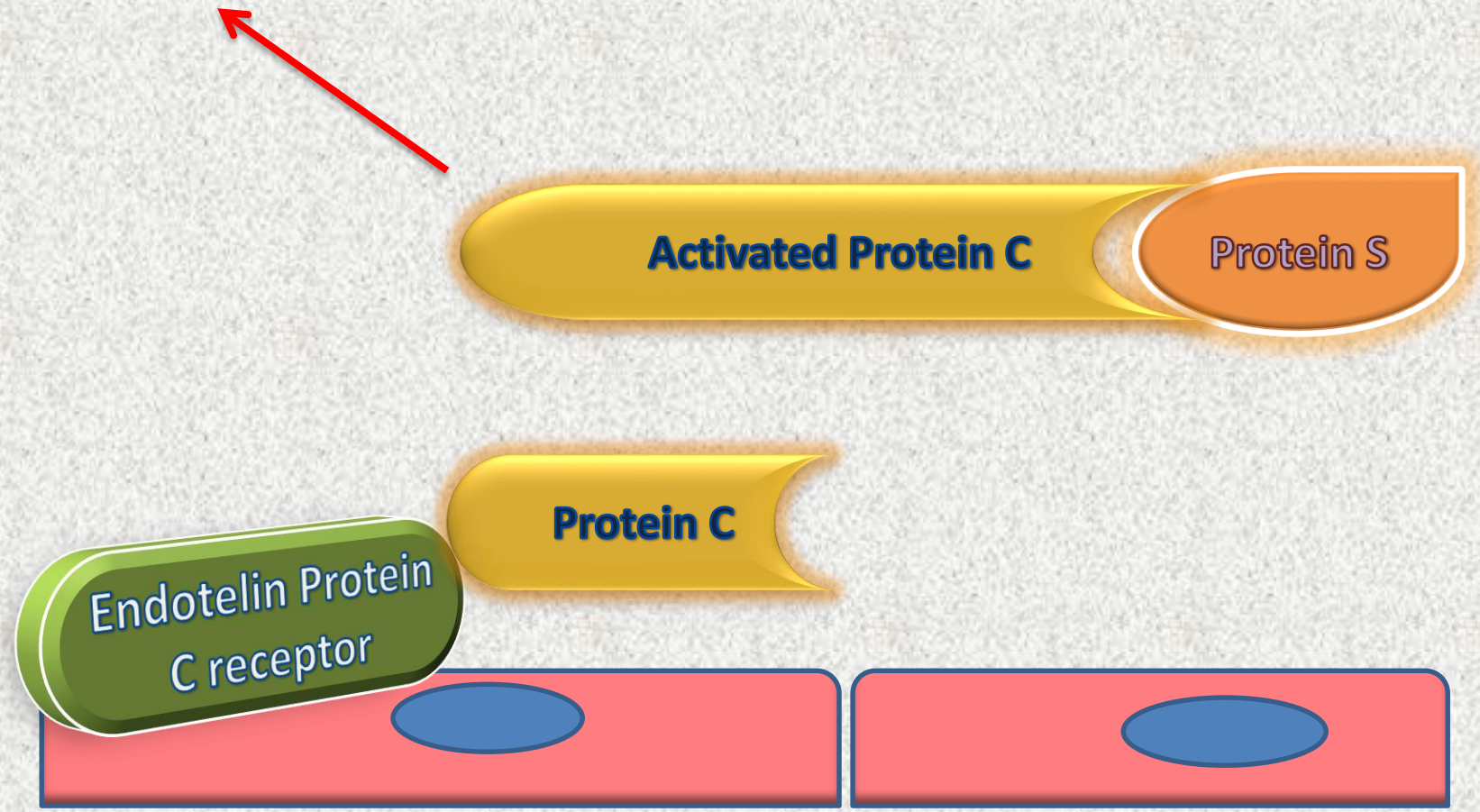
solubleEndothelial protein C Receptor (EPCR)

Soluble Vascular Cell Adhesion Molecule-1 (sVCAM)

lit-9

Journal of Blood Medicine 2018;9:1-7

Faktör V and Faktör VIII



Faktör V ve Faktör VIII

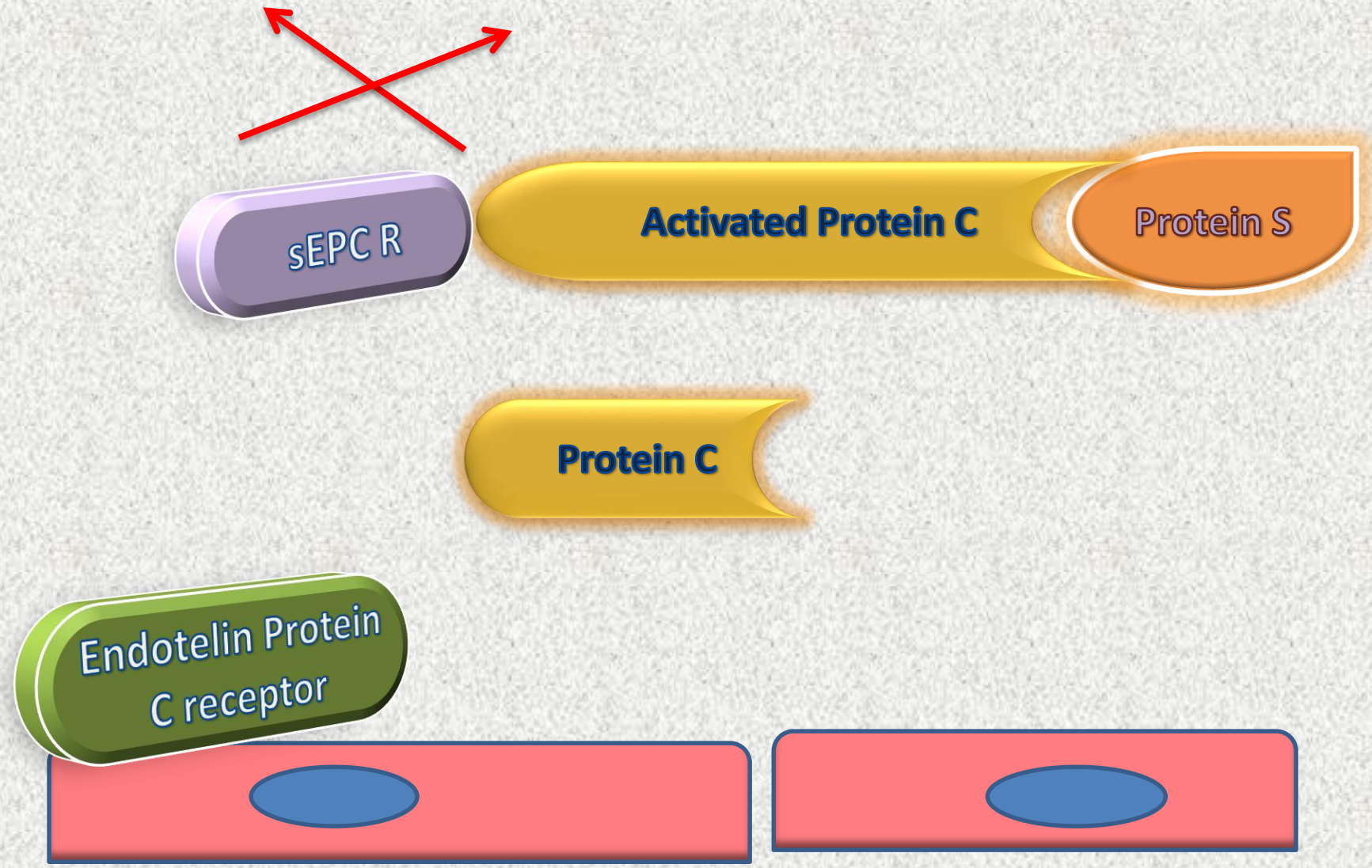


Table 1 Plasma levels of cytokines, PDMP, and soluble factors

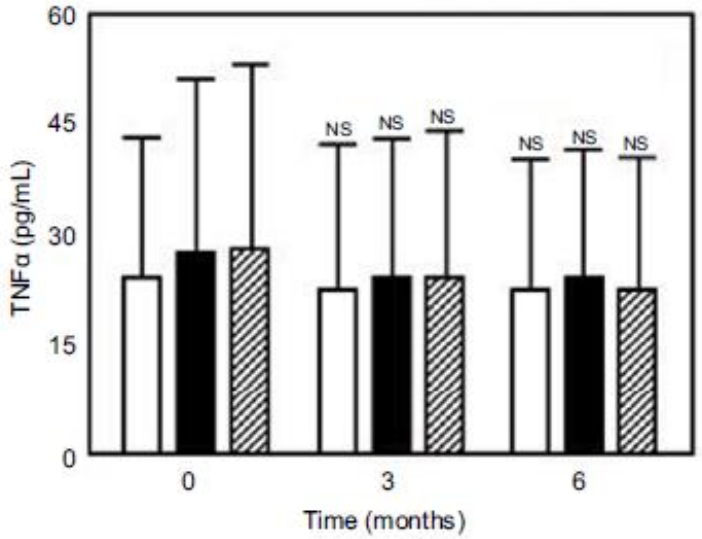
Biomarker	Controls (n=30)	Patients (n=103)
TNFα (pg/mL)	13.2±11.5	23.4±16.8^{NS}
HMGB1 (ng/mL)	3.1±0.9	9.9±1.2$^{p<0.001}$
PDMP (U/mL)	8.2±1.5	27.9±4.6$^{p<0.001}$
sVCAM-1 (ng/mL)	627±219	1,866±1,182$^{p<0.001}$
PAI-1 (ng/mL)	9.3±2.5	36.8±7.9$^{p<0.001}$
sEPCR (ng/mL)	84±25	180±68$^{p<0.001}$

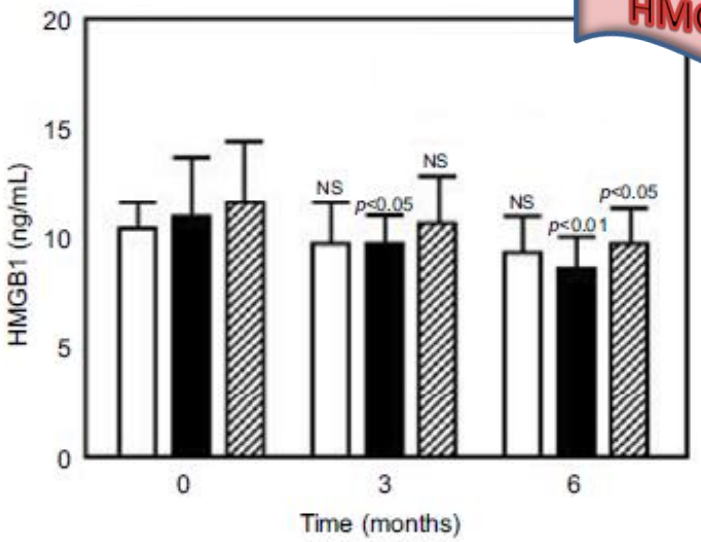
Notes: Data are shown as mean ± SD. *p*-value, patients versus controls.

Abbreviations: TNFα, tumor necrosis factor α; HMGB1, high mobility group box protein 1; PDMP, platelet-derived microparticles; sVCAM-1, soluble vascular cell adhesion molecule-1; PAI-1, plasminogen activator inhibitor-1; sEPCR, soluble endothelial protein C receptor; NS, not significant.

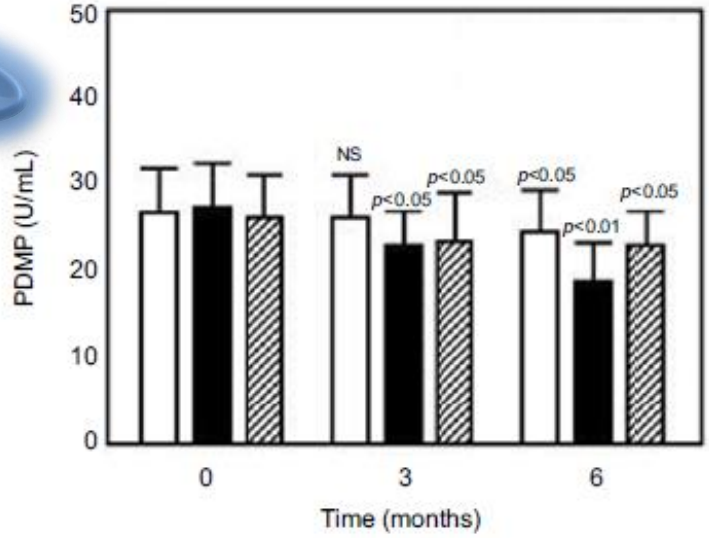
Journal of Blood Medicine 2018;9:1-7

HMGB1



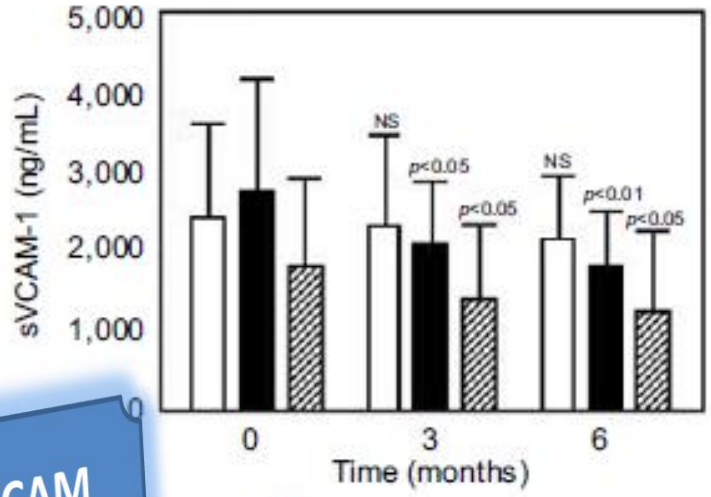


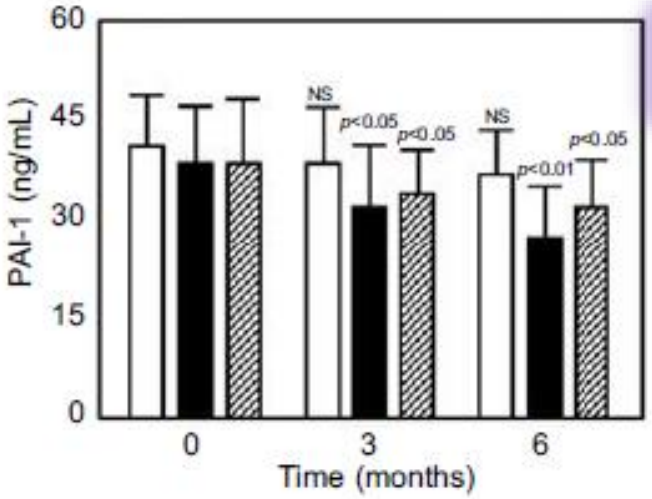
PDMP



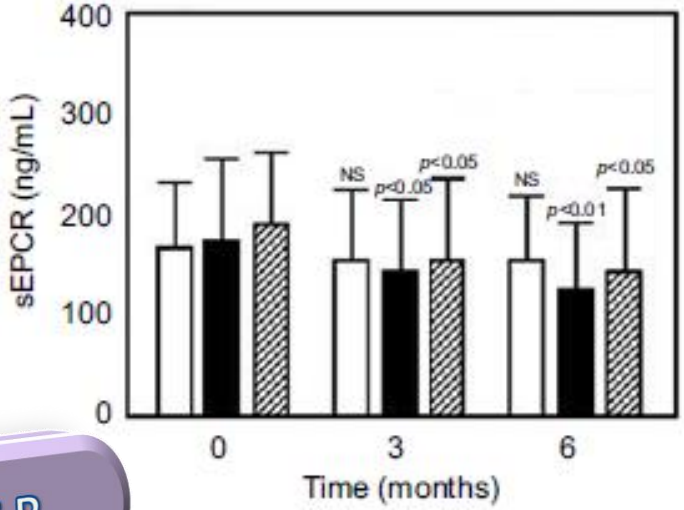
Journal of Blood Medicine 2018;9:1-7

PAI-1





sVCAM



sEPC R

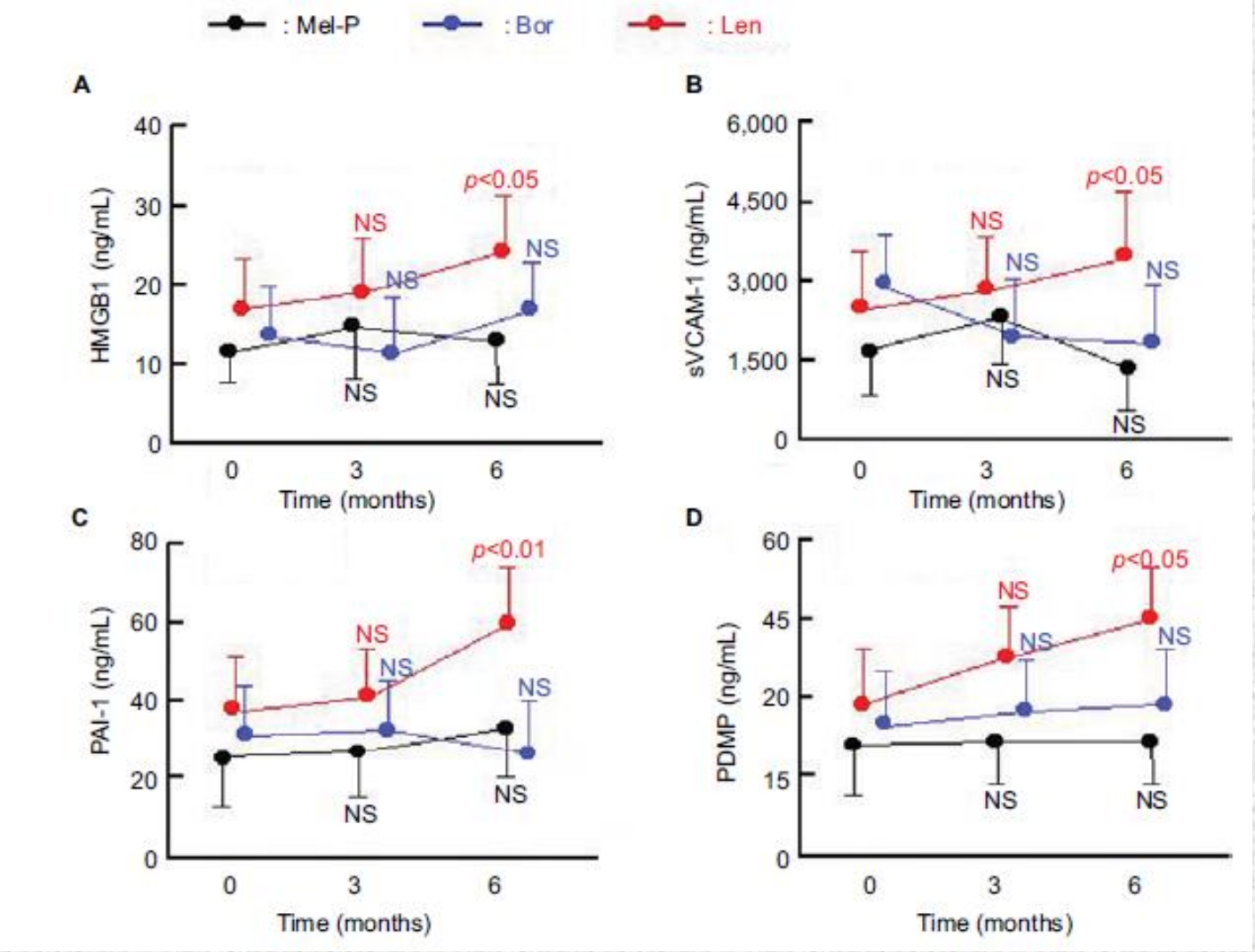
Journal of Blood Medicine 2018;9:1-7

sEPC R

Table 2 Changes in the plasma levels of PDMP, soluble factors, and cytokines/chemokines before and after all treatments of patients with elevated sEPCR

Biomarker	Before	3 months	6 months
HMGB1 (ng/mL)	15.1±4.9	15.8±5.2^{NS}	16.2±5.9^{NS}
sVCAM-1 (ng/mL)	2,230±1,060	2,295±1,102^{NS}	2,301±1,163^{NS}
PAI-1 (ng/mL)	31.5±19.6	32.3±21.2^{NS}	35.1±23.3^{NS}
PDMP (U/mL)	24.8±9.6	31.2±10.3^{NS}	32.1±11.4^{NS}

Journal of Blood Medicine 2018;9:1-7



Journal of Blood Medicine 2018;9:1-7

Original Article

Plasma Levels of Vascular Endothelial Growth Factor and Selected Hemostatic Parameters in Association With Treatment Response in Multiple Myeloma

Clinical and Applied Thrombosis/Hemostasis
Volume 25: 1-6

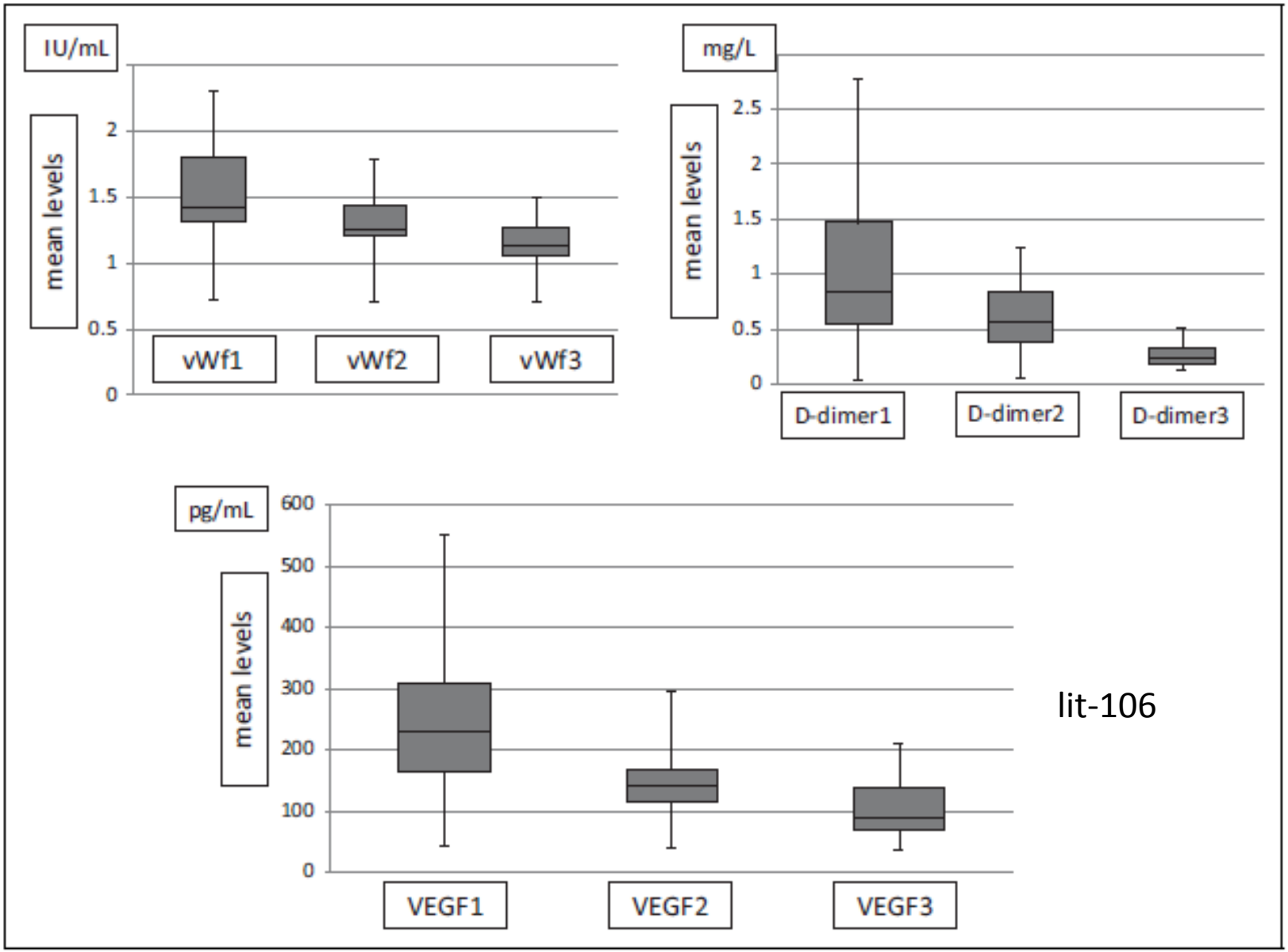
DOI: 10.1177/1076029618823280
journals.sagepub.com/home/cat
SAGE

Juraj Sokol, MD, PhD[1], Matej Hrncar, MD[1], Frantisek Nehaj, MD[2], and Jan Stasko, MD, PhD[1]

Yeni tanı ve relaps hastalar
36 hasta

Clinical and Applied Thrombosis/Hemostasis 2019;25:1-6

lit-106



lit-106

Clinical and Applied Thrombosis/Hemostasis 2019;25:1-6

Table 4. Results of Selected Parameters Before, During and After Treatment in Patients With Newly Diagnosed or Relapsed MM.

Characteristics	vWf1	vWf2	vWf3	D-Dimer1	D-Dimer2	D-Dimer3	VEGF1	VEGF2	VEGF3
Newly									
Number of patients	28	28	28	28	28	28	28	28	28
Mean	1.61	1.34	1.15	1.04	.61	.28	247.25	140.71	97.86
Median	1.50	1.28	1.12	.87	.57	.25	232	147	85
Standard deviation	.32	.2	.16	.63	.28	.12	128.11	44.67	41.29
Minimum	1.07	1.07	.70	.25	.16	.12	44	40	38
Maximum	2.3	1.79	1.5	2.78	1.24	.52	553	213	192
Relapsing									
Number of patients	8	8	8	8	8	8	8	8	8
Mean	1.24	1.22	1.19	.96	.56	.24	216.25	162.5	119.25
Median	1.27	1.23	1.23	.60	.44	.25	189.50	142.5	130.50
Standard deviation	.24	.24	.24	.92	.49	.09	111.68	80.21	57.15
Minimum	.72	.70	.7	.03	.06	.12	54	55	56
Maximum	1.58	1.51	1.5	2.27	1.25	.36	366	296	212

Abbreviations: MM, multiple myeloma; VEGF, vascular endothelial growth factor; vWf, von Willebrand factor.

Ayrıca Evre III de VTE riski en yüksek.

Düşüş Evre I dışında anlamlı.

lit-106

Clinical and Applied Thrombosis/Hemostasis 2019;25:1-6

Koagülasyon Faktörlerindeki Değişiklikler

Faktör VIII
von Willebrand Faktör

Protein S
Protein C

Table 3 Factor VIII levels in patients with MM, controls and different MM subgroups.

Patients with MM and controls	FVIII levels (IU/mL), median (range)	*P* value
Patients with MM at baseline control (no. 190)	2.23 (0.24–7.14)	<0.0001
Controls (no. 183)	1.61 (0.45–3.77)	
Patients with MM at baseline (no. 115)*	2.43 (0.24–7.14)	0.044
Patients with MM after thal–dex therapy (no. 115)*	2.31 (0.48–6.12)	
MM patients with stage III (n = 105)	2.35 (0.51–7.14)	0.059
MM patients with stages I or II (n = 76)	2.04 (0.24–5.84)	
Responders (n = 94) to thal–dex*	2.34 (0.48–6.12)	0.948
Non-responders (n = 21) to thal–dex*	2.10 (0.85–5.11)	
MM patients with VTE (n = 15)	2.59 (0.86–5.17)	0.564
MM patients without VTE (n = 166)	2.22 (0.24–7.14)	

European Journal of Haematology 2010;84: 484-492

Table 2. Screening Tests of Hemostasis

Parameter	Patients	Controls	Abnormality in patients	
	Mean±SD	Mean±SD	No.	%
PT (secs)	14.1±3.3*	12.4±0.9*	14	48.3
APTT (secs)	39.6±10.1*	29.6±1.3*	20	68.9
TT (secs)	11.3±2.7*	9.8±0.5*	10	34.5

* $p<0.01$, significant; SD, Standard Deviation; PT, Prothrombin Time; APTT, Activated Partial Thromboplatin Time; TT, Thrombin Time.

Lit-10

Asian Pac J Cancer Prev 2018;19(1):127-130

Table 3. Plasma Fibrinogen and Factor VIII

Parameter	Mean± SD		p-value
	Patients	Controls	
Fibrinogen (mg/dl)	272.9±185.6	225.0±58.7	p=0.194; not significant
Factor VIII (%)	63.5±45.8	102.8±28.4	p<0.01; significant

29 hasta

Lit-10

Asian Pac J Cancer Prev 2018;19(1):127-130

Table 4. Abnormal Tests of Hemostasis

Parameter	Cut off values	Patients	
		Number	Percentage %
Fibrinogen(mg/dl)	<150	11	37.9
	>400	10	34.5
Factor VIII(%)	<50	11	37.9
	>170	1	3.4
D-dimer(ng/ml)	>400	22	75.9

Lit-10

Asian Pac J Cancer Prev 2018;19(1):127-130

- **Kanamaya eğilimi gösteren markerlar**

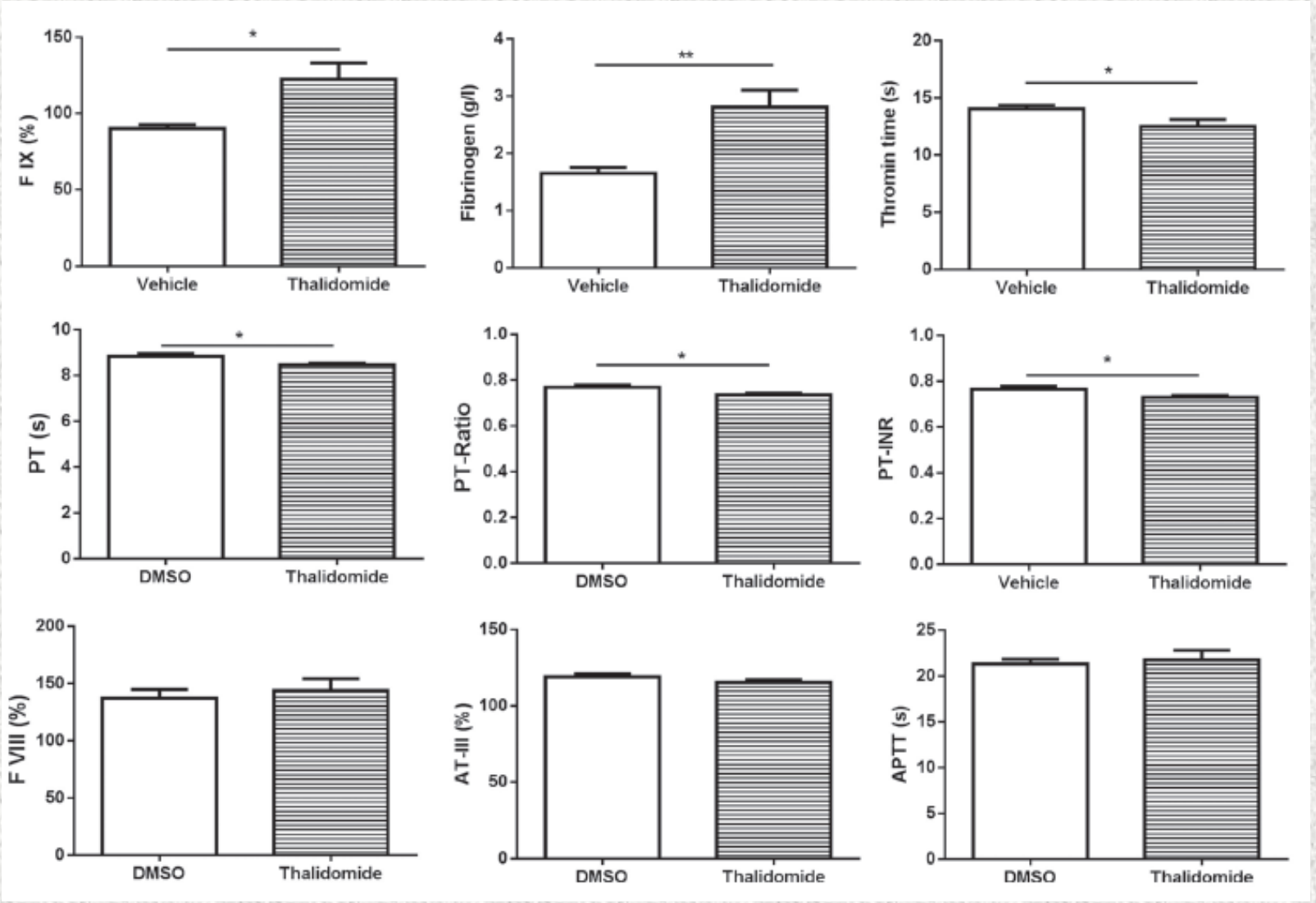
  Trombositopeni, uzamış PT, PTT, TT, düşük fibrinojen, FVIII'den en az biri var**…… %27.6**

- **Tromboza eğilimi gösteren markerlar**

  Artmış FVIII, fibrinojen, D-dimer, LA**……%82.7**

29 Hastanın %100'ünde en az bir marker bozuk

Lit-10



Talidomid

Lit-15

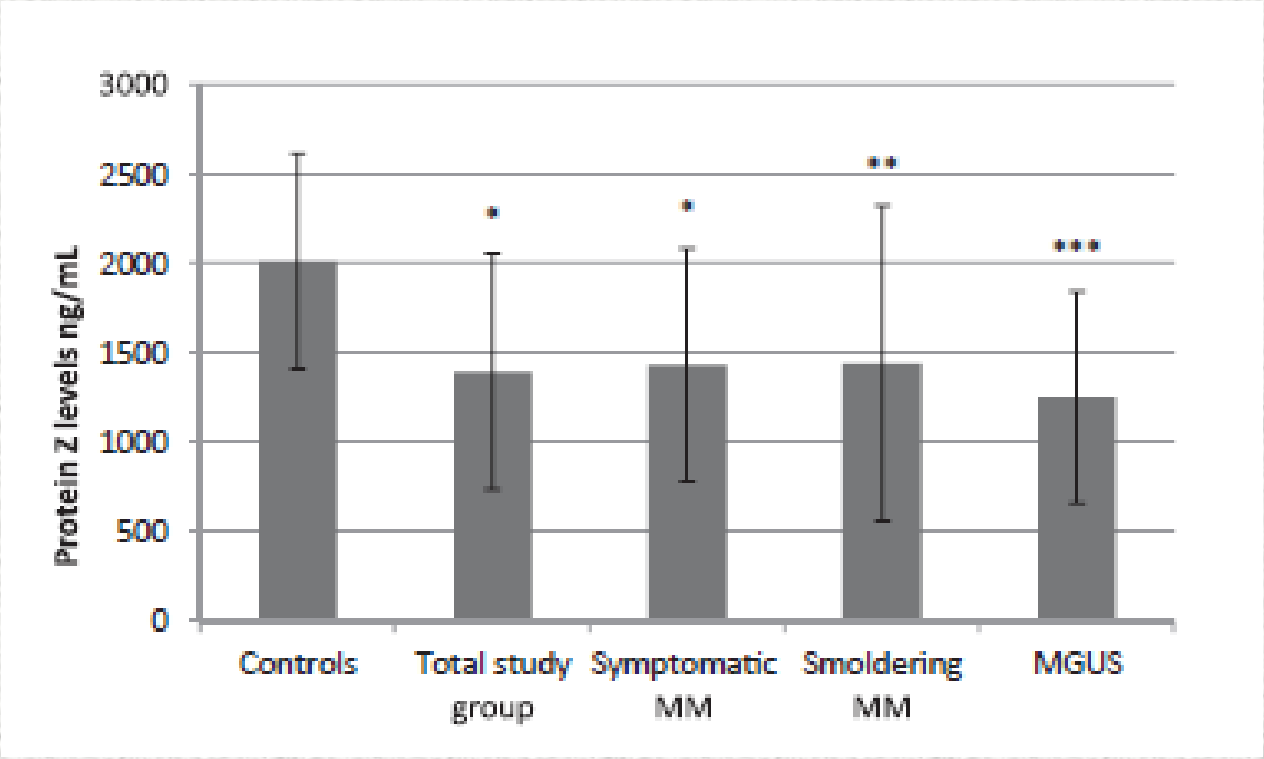
Oncotarget, 2017, Vol. 8, (No. 22), pp: 35776-35782

PZ: Protein Z

PZI: Protein Z dependent inhibitor

Lit-11

PZ: Protein Z



Lit-11

Leukemia Research 2017;62:104-107

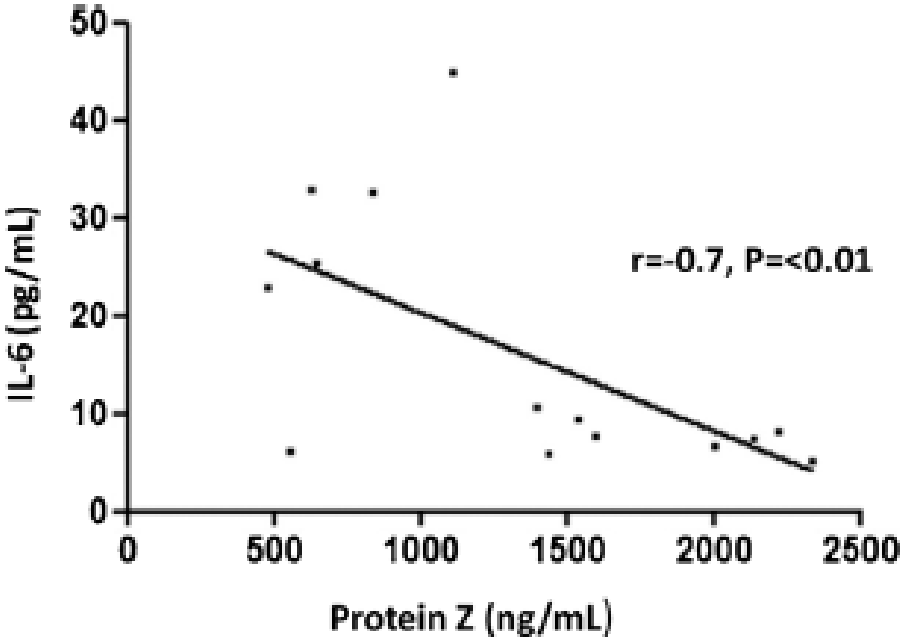
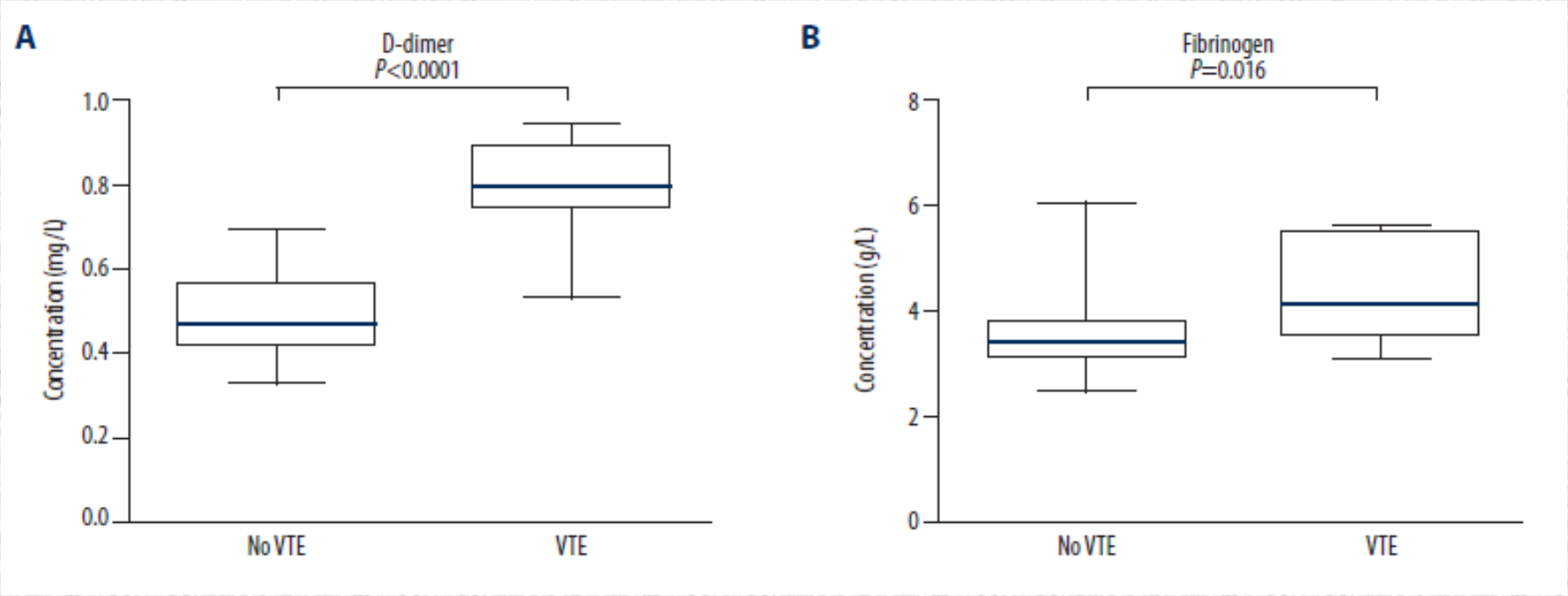


Fig. 2. Correlation between Protein Z and IL-6.

Lit-11

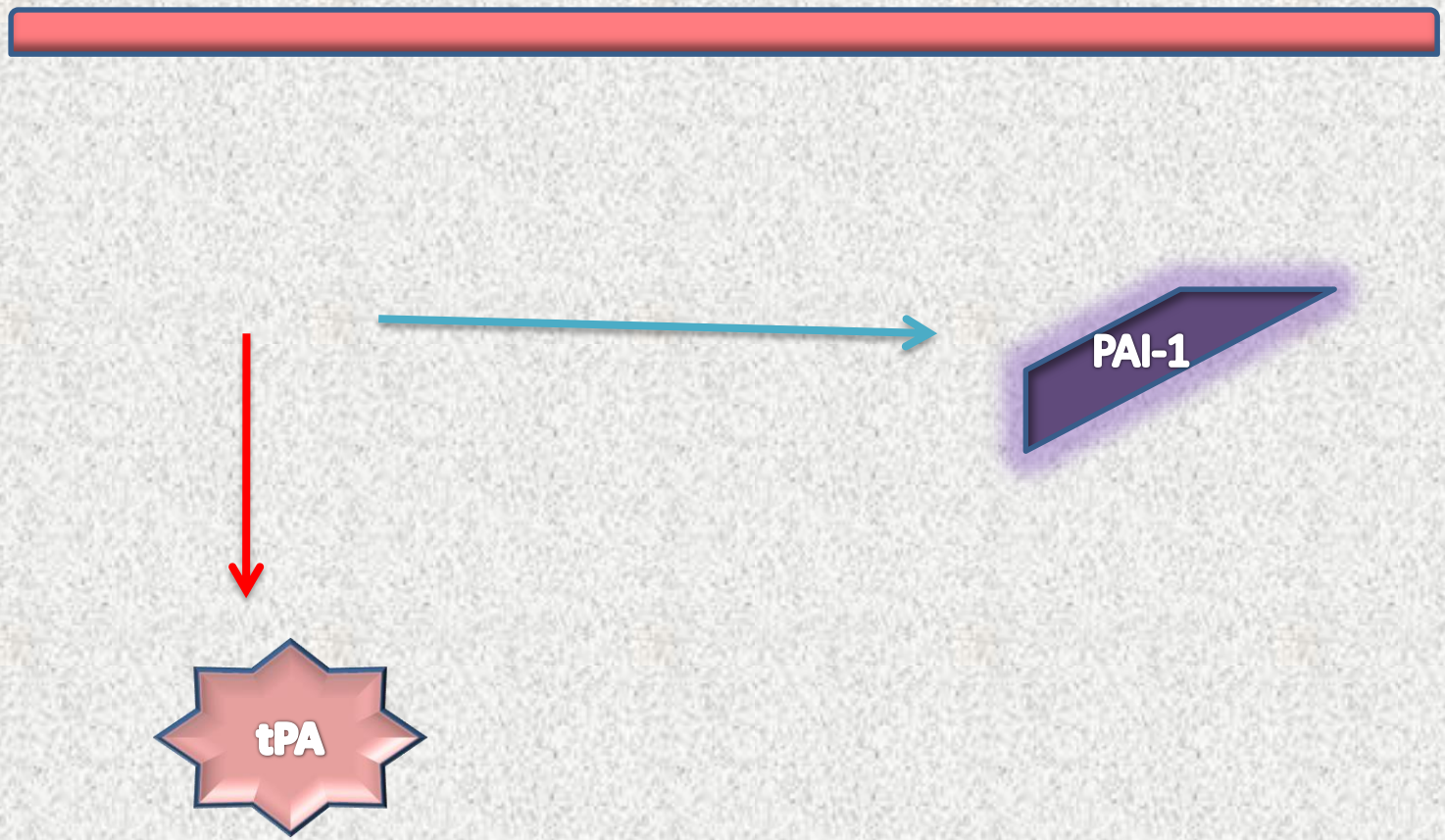


Thalidomide ilişkili VTE
hasta n= 313
VTE : 7

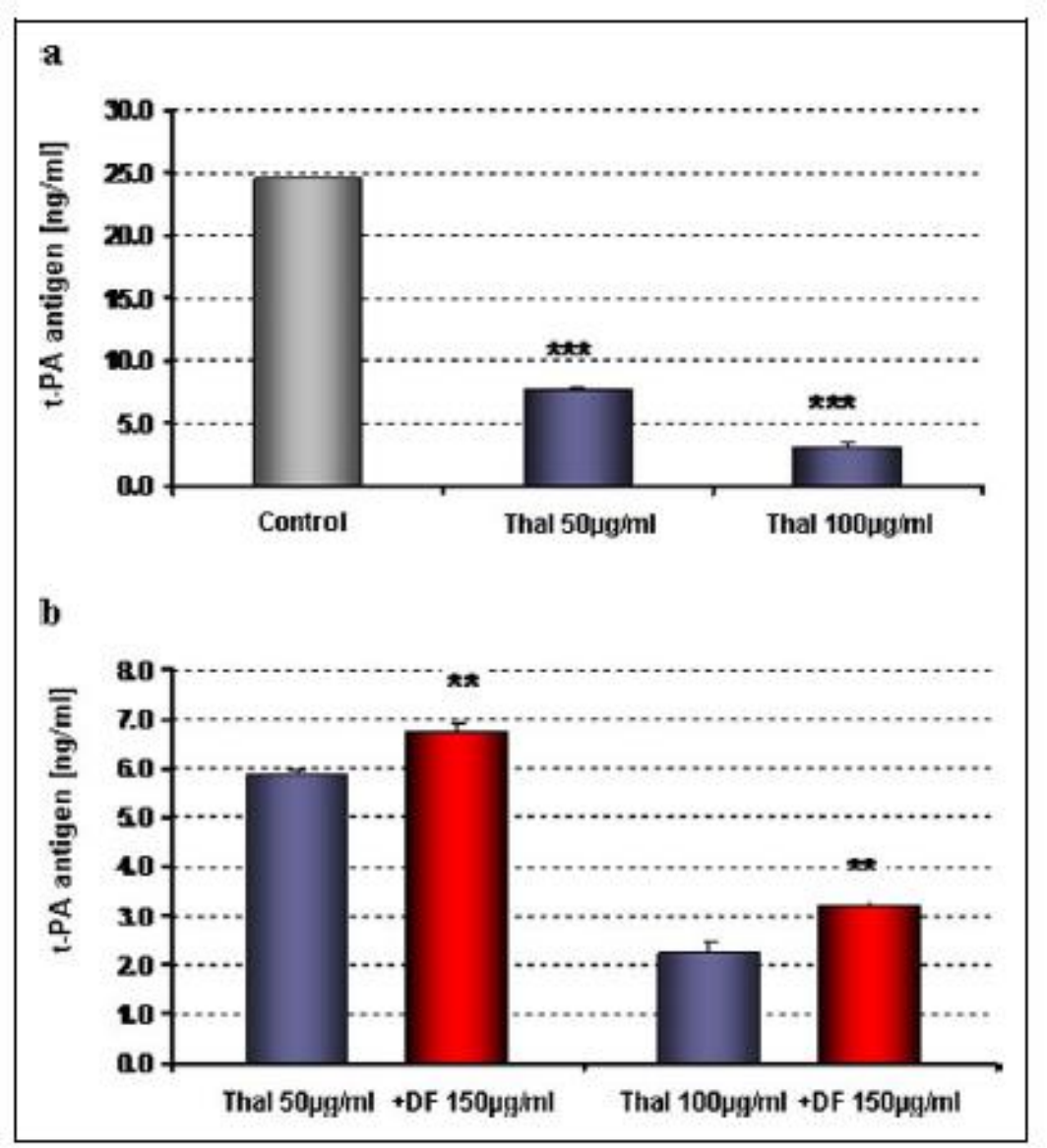
Lit-21

Med Sci Monit 2016;22:3835-3842

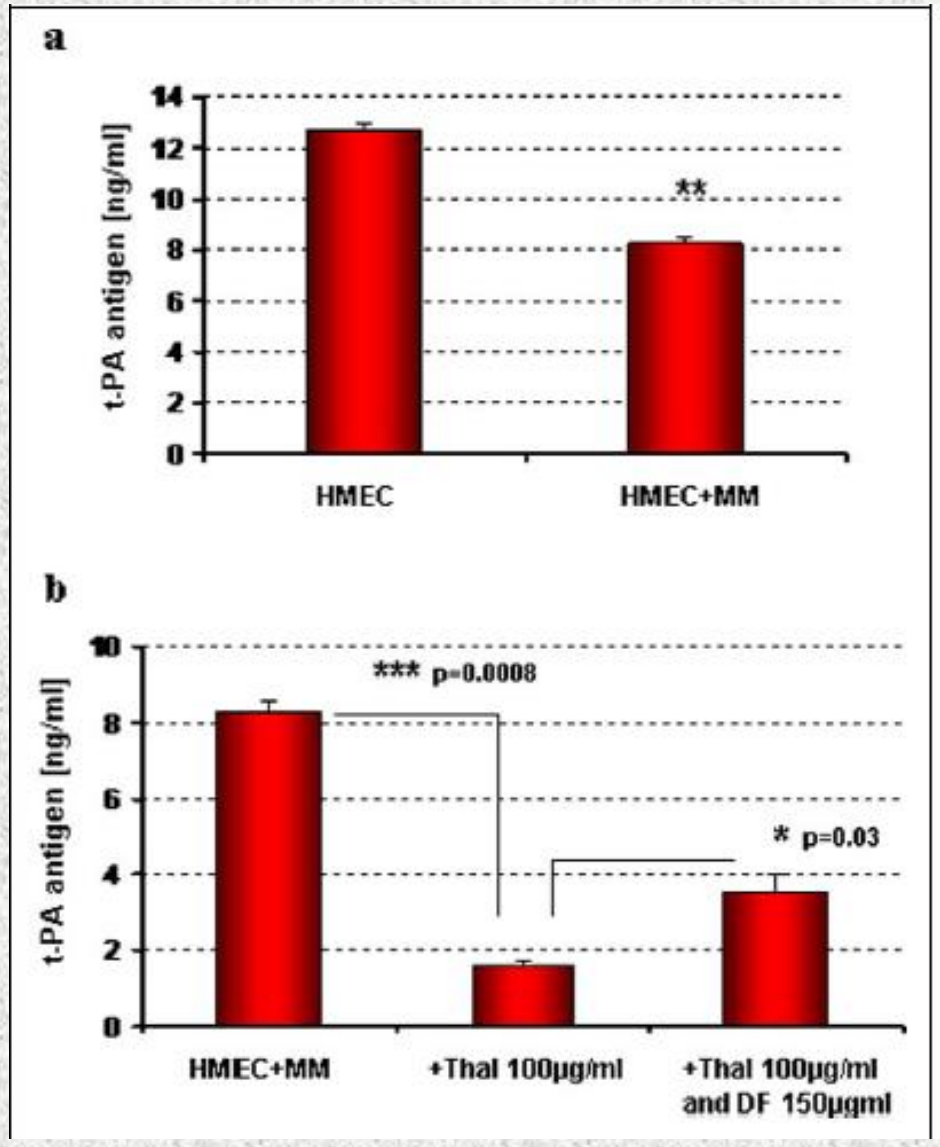
Fibrinoliz



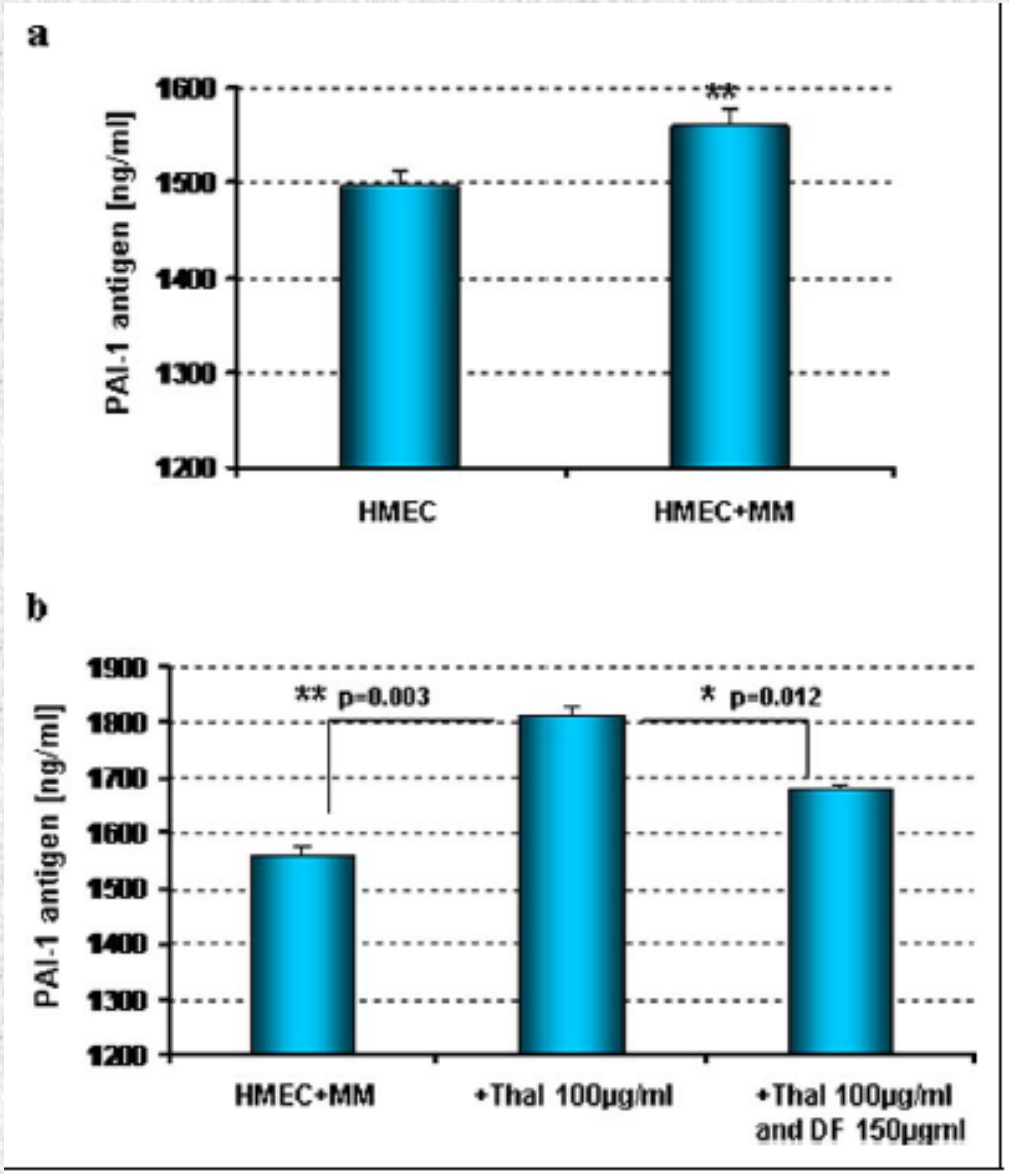
Clin and Applied Thrombosis/ Hemostasis 2012;18(1):79-86



Clin and Applied Thrombosis/ Hemostasis 2012;18(1):79-86

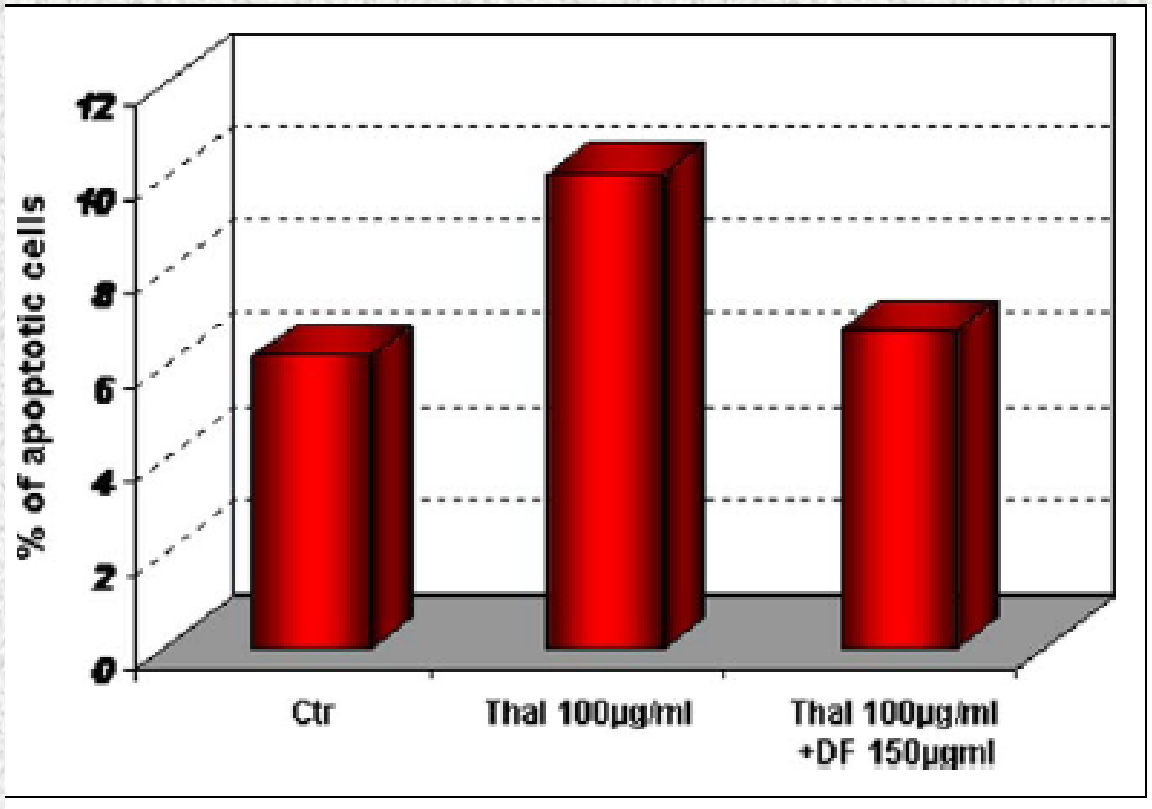

a
t-PA antigen [ng/ml]
14
12
10
8
6
4
2
0
**
HMEC
HMEC+MM
b
t-PA antigen [ng/ml]
10
8
6
4
2
0
*** p=0.0008
* p=0.03
HMEC+MM
+Thal 100µg/ml
+Thal 100µg/ml and DF 150µgml


tPA



PAI-1

Clin and Applied Thrombosis/ Hemostasis 2012;18(1):79-86



Clin and Applied Thrombosis/ Hemostasis 2012;18(1):79-86

Trombositler

Tedavi dozunda Thalidomide,

platelet aktivasyonunu (*in vitro* ve *in vivo) ETKİLEMEDİ*

Oncotarget, 2017, Vol. 8, (No. 22), pp: 35776-35782

Lit-15

Thalidomide tedavisi

GPIbα, GPVI, α_{IIb} β_3 ekspresyonunu veya

Collagen, ADP-induce platelet agregasyonunu etkilemedi

platelet P-selectin ekspresyonunda artış olmadı

Oncotarget, 2017, Vol. 8, (No. 22), pp: 35776-35782

Talidomit tedavisinin 4. haftasından sonra

PAC-1'ın artmış ekspresyonu gözlendi

PAC-1 (antibody that recognizes conformational change of the GPIIb/IIIa)

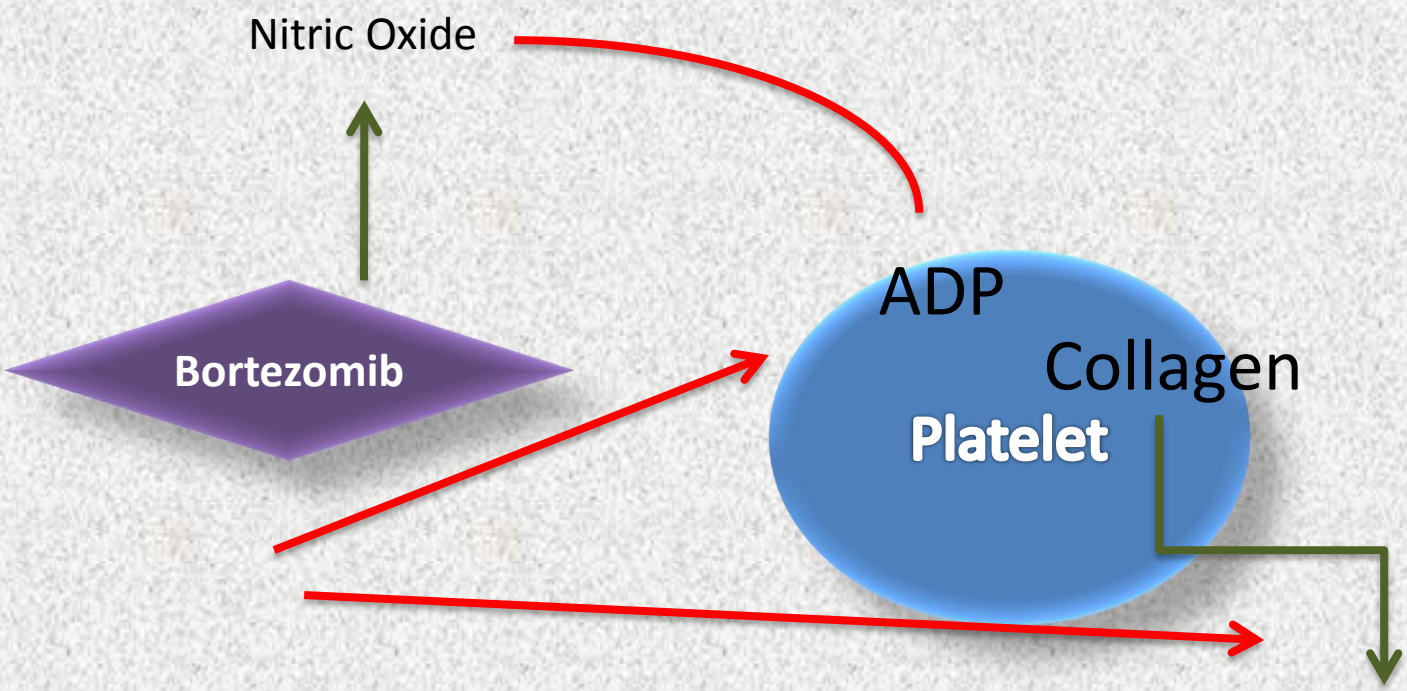
Blood Coagul Fibrinolysis 2013;24:893-895

Lit-30

Bortezomib:

Proteasome inhibitor.

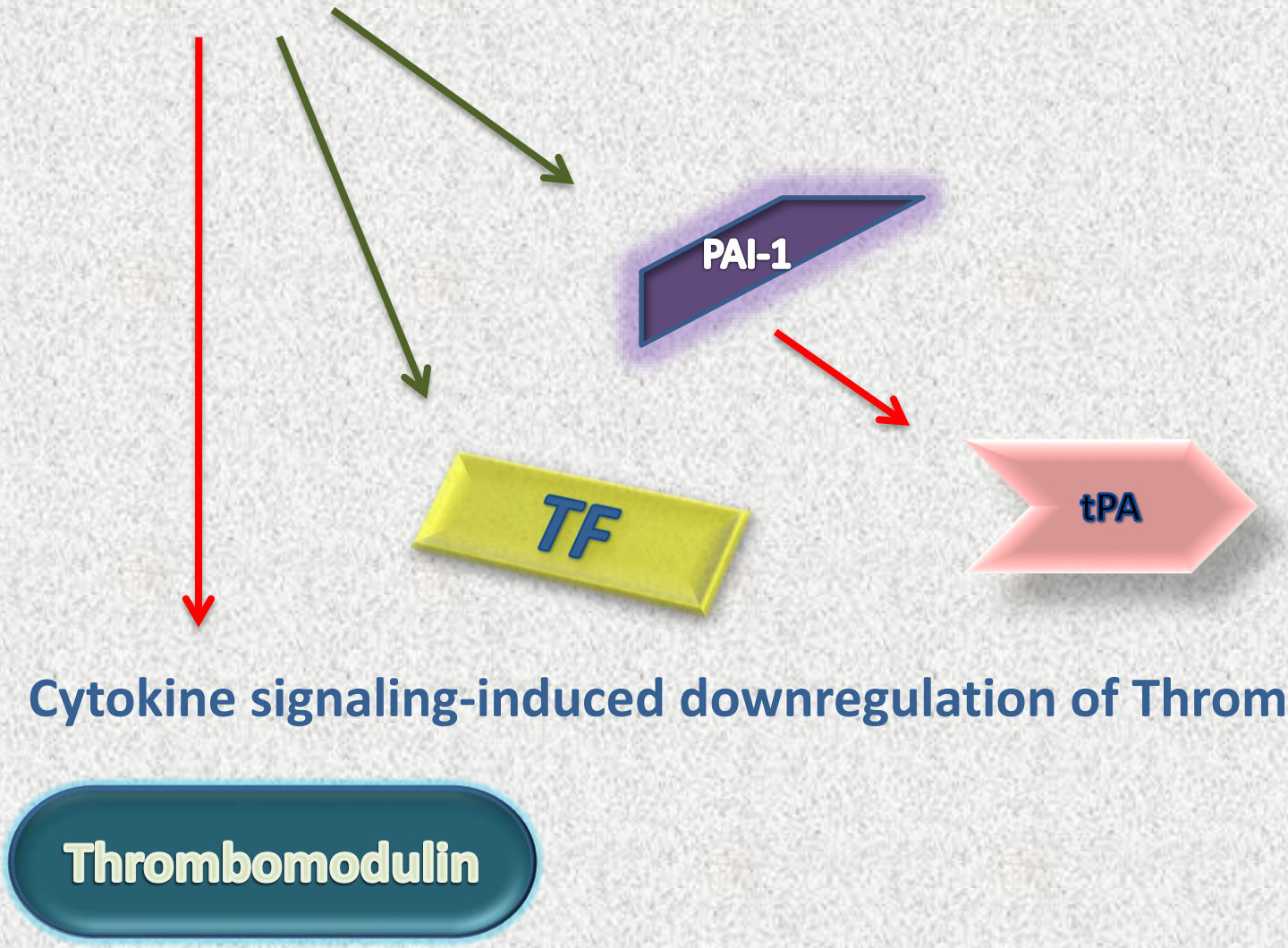
nuclear factor-κβ (NF κβ) aktivitesinin inhibisyonu



Colagen induced ATP release

Nitric Oxide ADP reseptör inhibisyonu üzerinden

trombosit aktivasyonun azaltır



Cytokine signaling-induced downregulation of Thrombomodulin

Thrombomodulin

ORIGINAL ARTICLE

ISLH International Journal of Laboratory Hematology WILEY

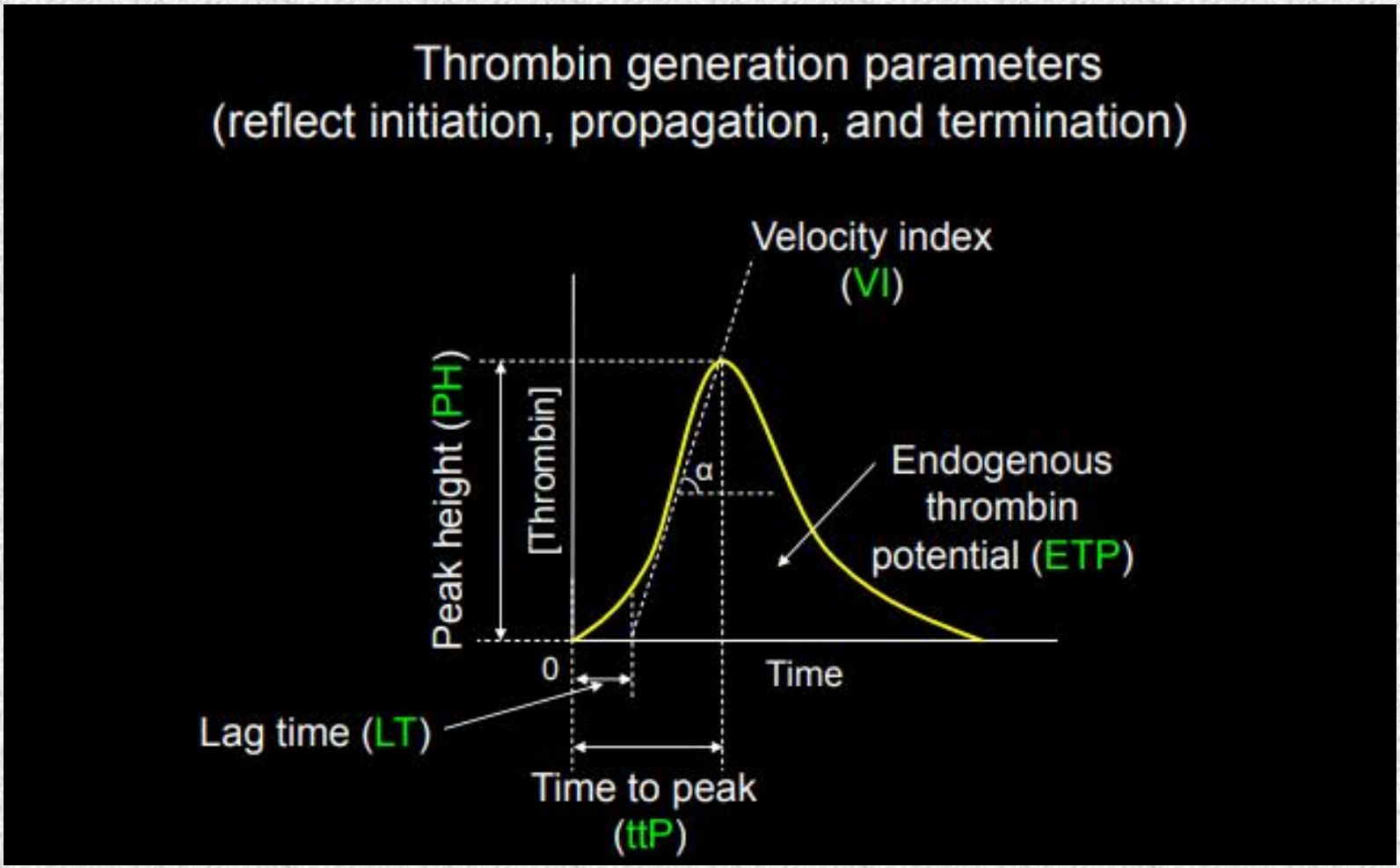
The hypercoagulable state in multiple myeloma: The contribution of thrombin generation test

Hela Baccouche[1,2] | Meriam Hadhri[1] | Wafa Aissi[2,3] | Aya Chakroun[1,2] | Dhouha Bahri[1] | Sonia Mahjoub[1,2] | Neila Ben Romdhane[1,2]

the lag time (min), the time to peak (TtPeak, min), the peak (nmol/L), the endogenous thrombin potential (ETP, nmol/L × min), and the velocity index (nmol/L/min).

Int J Lab Hematol. 2019;00:1-7

Lit-101


Thrombin generation parameters
(reflect initiation, propagation, and termination)
Velocity index
(VI)
Peak height (PH)
[Thrombin]
α
Endogenous
thrombin
potential (ETP)
0
Time
Lag time (LT)
Time to peak
(ttP)

Tissue Factor Concentration 5 PM

lit-101

Thrombogram parameters	Patients (n = 31)	Controls (n = 31)	*P*
	TF 5 PM		
Lag time (min)	2.4 (2-2.9)	2.7 (2.4-3)	.1
TtPeak (min)	4.4 (3.8-4.8)	5 (4.5-6)	.005
Peak (nmol/L)	323 (259-345)	285 (235-352)	.2
ETP (nmol/L/min)	1230 (1083-1541)	1269 (1169-1481)	.4
VI (nmol/L/min)	178 (131-200)	128 (96-161)	.013

ETP, endogenous thrombin potential; TF, tissue factor; TtPeak, time to peak; VI, velocity index.

ETP, yüksek riskli hastalarda, düşük risklilere göre istatiksel olarak daha yüksek

Int J Lab Hematol. 2019;00:1-7

Genetik

Aspirin profilaksisi alan hastalarda,

NFβ1 (rs3774968) genindeki

single-nucleotide polymorphism

artmış VTE riski ile ilişkili bulundu.

American Journal of Hematology 2013;88:765-770

Genetic

TABLE IV. Association of SNPs with VTEs

	VTE (% of patients with the specific genotype who developed VTE)	*P* value
ALDH1A1 (rs610529)		
T/T	4.2%	0.576
C/T or C/C	8.3%	
CHEK1 (rs506504)		
T/T or C/T	8%	0.951
C/C	8.5%	
CINP (rs7011)		
C/C	8.2%	0.927
C/T or T/T	7%	
NFKB1 (rs3774968)		
C/C or C/T	6%	0.051
T/T	16.7%	
TNFRSF17(rs19222317)		
A/A	5.6%	0.120
A/G or G/G	11.5%	
XRCC5 (rs2440)		
C/C or C/T	7.1%	0.434
T/T	11.5%	
CDKN1A (rs3829963)		
C/C	10%	0.330
C/A or A/A	3.8%	

American Journal of Hematology 2013;88:765-770

Profilaksi

Recommendations for VTE prophylaxis in myeloma patients based on risk factors

Both individual and myeloma-related risks of VTE should be taken into account in determining the type of thromboprophylaxis.

- If no risk factor, or any one risk factor is present, aspirin 81-325 mg once daily is recommended.
- If two or more risk factors are present, LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin, international normalized ratio (INR) 2-3, is recommended.
- If any myeloma therapy-related risk factor is present, then LMWH (equivalent of 40 mg enoxaparin once daily) or full-dose warfarin (target INR 2-3) is recommended.

Recommendations for VTE prophylaxis in myeloma patients based on type of therapy

- Thalidomide
  - Patients receiving single-agent thalidomide: anticoagulation therapy not recommended
  - Newly diagnosed patients receiving thal/dex: full-dose warfarin
  - Newly diagnosed patients treated with combinations that include melphalan (i.e. MPT): low-molecular-weight heparin (LMWH)
  - Newly diagnosed patients treated with thalidomide + multiagent chemotherapies: LMWH, low-fixed-dose warfarin, and full-dose aspirin **not effective**
  - Newly diagnosed patients treated with thal + doxorubicin when the regimen contains bortezomib: LMWH effective
  - Relapsed patients: anticoagulant prophylaxis suggested only in those with a high risk of VTE

- Lenalidomide
  - Patients receiving single-agent lenalidomide: anticoagulation therapy not recommended
  - Patients receiving lenalidomide plus low-dose dexamethasone, melphalan, or doxorubicin: aspirin recommended (if no or one risk factor present)
  - Patients receiving high-dose dexamethasone: LMWH or full-dose warfarin recommended

Clinical characteristics	DOAC			Warfarin
Diagnosis—no. (%)				
Multiple myeloma	18 (72%)			34 (94%)
Lymphoma	4 (16%)			2 (6%)
Myelodysplastic syndrome	1 (4%)			0
Plasma cell leukemia	1 (4%)			0
Scleromyxedema	1 (4%)			0
Immunomodulatory agent—no. (%)				
Lenalidomide	21 (84%)	25	36	32 (89%)
Thalidomide	1 (4%)			0
Pomalidomide	3 (12%)			4 (11%)
Concomitant antineoplastic therapy—no. (%)				
None	10 (40%)			8 (22%)
Dexamethasone	11 (44%)			26 (72%)
Dexamethasone + proteasome inhibitor	7 (28%)			10 (28%)
Doxorubicin	1 (4%)			0
Rituximab	3 (12%)			2 (6%)
Prior VTE—no. (%)	16 (64%)			25 (69%)
Thrombotic risk factors—no.[a]				
0–1	3			2
≥2	22			34

lit-12

J Thrombosis Thrombolysis 2017;44:298-302

DOAC—no. (%)		Not applicable
Dabigatran	3 (12%)	
Rivaroxaban	15 (60%)	
Apixaban	7 (28%)	
DOAC dosing level—no. (%)		Not applicable
Prophylactic	8 (32%)	
Therapeutic	17 (68%)	
Concomitant antiplatelet therapy—no. (%)		
None	18 (72%)	32 (89%)
ASA 81 mg	7 (28%)	2 (5.5%)
ASA 325 mg	0	2 (5.5%)

lit-12

J Thrombosis Thrombolysis 2017;44:298-302

Table 3 Outcomes of patients in the DOAC and warfarin groups

Outcomes	DOAC	Warfarin
Bleeding events—no. (%)	4 (16%)	6 (17%)
Fatal bleed	0	0
Major bleed	0	2 (6%)[a]
Non-major bleed	4 (16%)	4 (11%)
Gastrointestinal	1 (4%)[a]	0
Hematuria	1 (4%)[b]	0
Bruising	1 (4%)[b]	1 (3%)[b]
Epistaxis	1 (4%)[a]	2 (6%)[a]
Extremity hematoma	0	1 (3%)[a]
Thrombotic events—no. (%)	1 (4%)	0

lit-12

J Thrombosis Thrombolysis 2017;44:298-302

Received: 8 February 2019 | Revised: 7 March 2019 | Accepted: 8 March 2019

DOI: 10.1002/ajh.25459

RESEARCH ARTICLE

AJH WILEY

Apixaban for the prevention of thromboembolism in immunomodulatory-treated myeloma patients: Myelaxat, a phase 2 pilot study

Brigitte Pegourie[1] | Lionel Karlin[2] | Lotfi Benboubker[3] | Frédérique Orsini-Piocelle[4] | Mourad Tiab[5] | Sophie Auger-Quittet[6] | Philippe Rodon[7] | Bruno Royer[8] | Xavier Leleu[9] | Benoit Bareau[10] | Manuel Cliquennois[11] | Jean-Gabriel Fuzibet[12] | Eric Voog[13] | Karim Belhadj-Merzoug[14] | Olivier Decaux[15] | Philippe Rey[16] | Bohrane Slama[17] | Cecile Leyronnas[18] | Charles Zarnitsky[19] | Eileen Boyle[20] | Jean Luc Bosson[21] | Gilles Pernod[22] | for the IFM Group

Lit-105

Am J Hematol. 2019;94:635-640

TABLE 1 Main patients' characteristics at study entry (n = 104)

Mean age (y) ± SD	69.8 ± 7.8
Gender	Male 56 (51.8%)/ Female 52 (48.2%)
Creatinine clearance (Cockcroft, ml/min)	
<30	0
30-50	14 (13.5%)
>50	87 (83.6%)
NA	3
BMI (mean, SD)	26.2 (4.8)
Myeloma	
IgG	61.5%
IgA	21.1%
IgD	0.01%
Light chain	16.3%
First line	10.6%
Relapse	89.4%
First relapse	76.3%
Thrombotic assessment	
High risk	14%
Low risk	86%

Thrombotic assessment was based on IMWG criteria.

MPT

LD

Am J Hematol. 2019;94:635-640

TABLE 2 Clinical outcomes during the treatment period

Outcomes	Number of patients (n = 104)	VTE risk assessment according to IMWG
Efficacy		
VTE event	2	
VTE related death	0	
Type of VTE event		
Asymptomatic proximal DVT	1	Low risk
Symptomatic distal DVT	1	High risk[a]
Safety		
Major bleeding	1	Low
Fatal bleeding	0	
Intracranial	0	
Nonfatal major bleeding (epistaxis)	1	
Clinically relevant nonmajor bleeding	10	
Epistaxis	2	Low
Gastrointestinal	4	Low
Genito-urinary	3	Low
Hematoma	1	High[a]

Abbreviations: VTE, venous thromboembolic disease; DVT, deep vein thrombosis. The asymptomatic proximal DVT was discovered on CUS at month 3, while patient was responder to Lenalidomide-Dexamethasone.

[a]Denotes the both outcome in a same patient.

Am J Hematol. 2019;94:635-640

Lit-105

TABLE 3 Incidence of VTE in Myelaxat study (% pt-mths)

Carrier first line LMWH prophylaxis	Carrier relapse any prophylaxis	Myelaxat total (N = 104)	Myelaxat relapse (N = 93)
2.1 (1.1-3.6)	0.7 (0.5–1.1)	0.38 (0.05-1.40)	0.43 (0.05-1.45)

Abbreviation: VTE, venous thromboembolic disease.

Incidence (95% CI) of VTE events was calculated for the entire population and for the patients in relapse because they represent the main population. Incidence of VTE depicted in Carrier's meta-analysis was also reported for first line and relapse.

Am J Hematol. 2019;94:635-640

frontiers in Oncology

METHODS
published: 26 February 2019
doi: 10.3389/fonc.2019.00045

Apixaban for Primary Prevention of Venous Thromboembolism in Patients With Multiple Myeloma Receiving Immunomodulatory Therapy

Robert Frank Cornell[1], Samuel Z. Goldhaber[2], Brian G. Engelhardt[1], Javid Moslehi[3], Madan Jagasia[1], Daryl Patton[4], Shelton Harrell[1], Robert Hall[1], Houston Wyatt[1] and Greg Piazza[2]*

NCT02958969

Lit-104

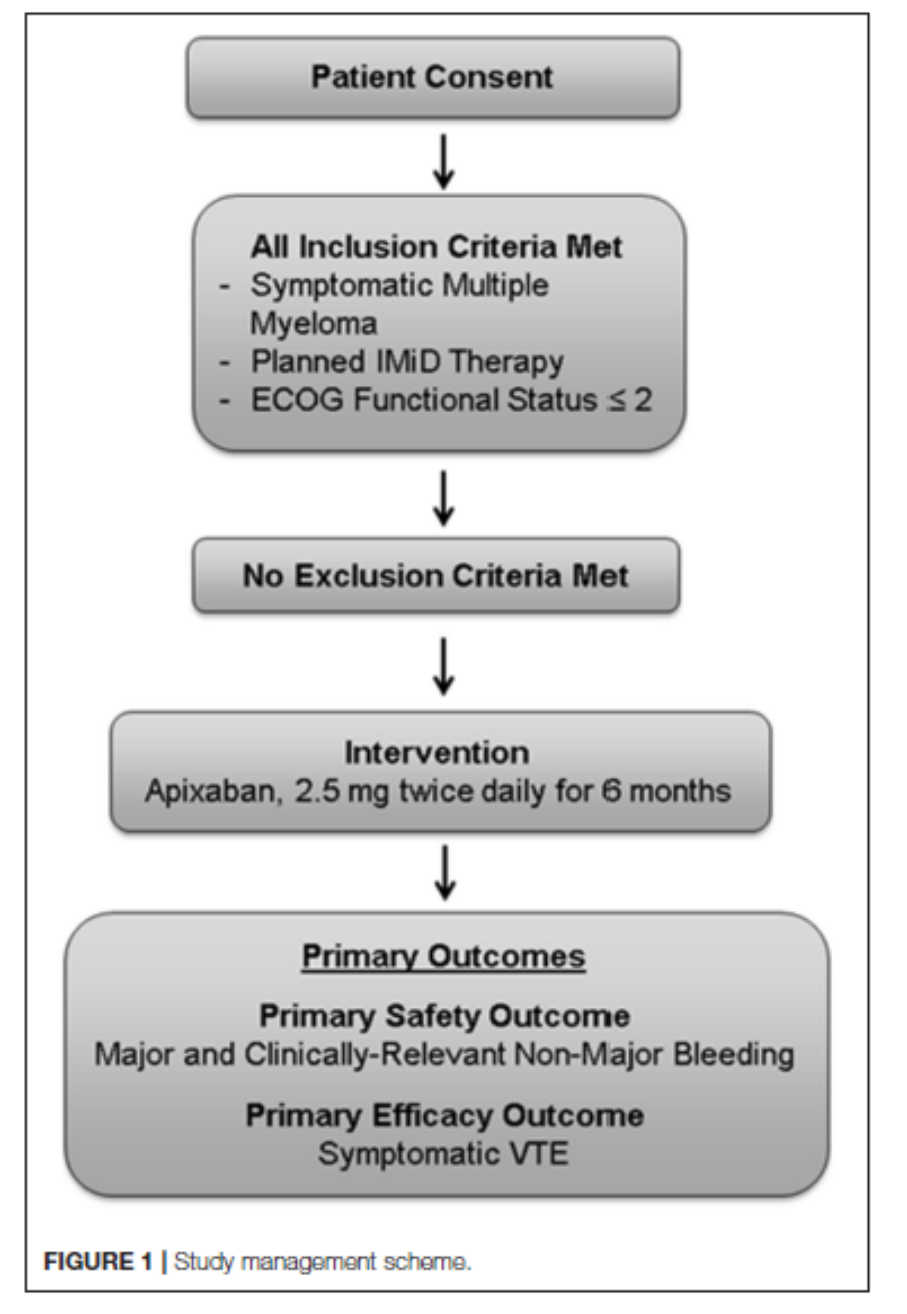


FIGURE 1 | Study management scheme.

NCT02958969

Lit-104

HİPOTEZLERİ

6 aylık VTE riski < %5

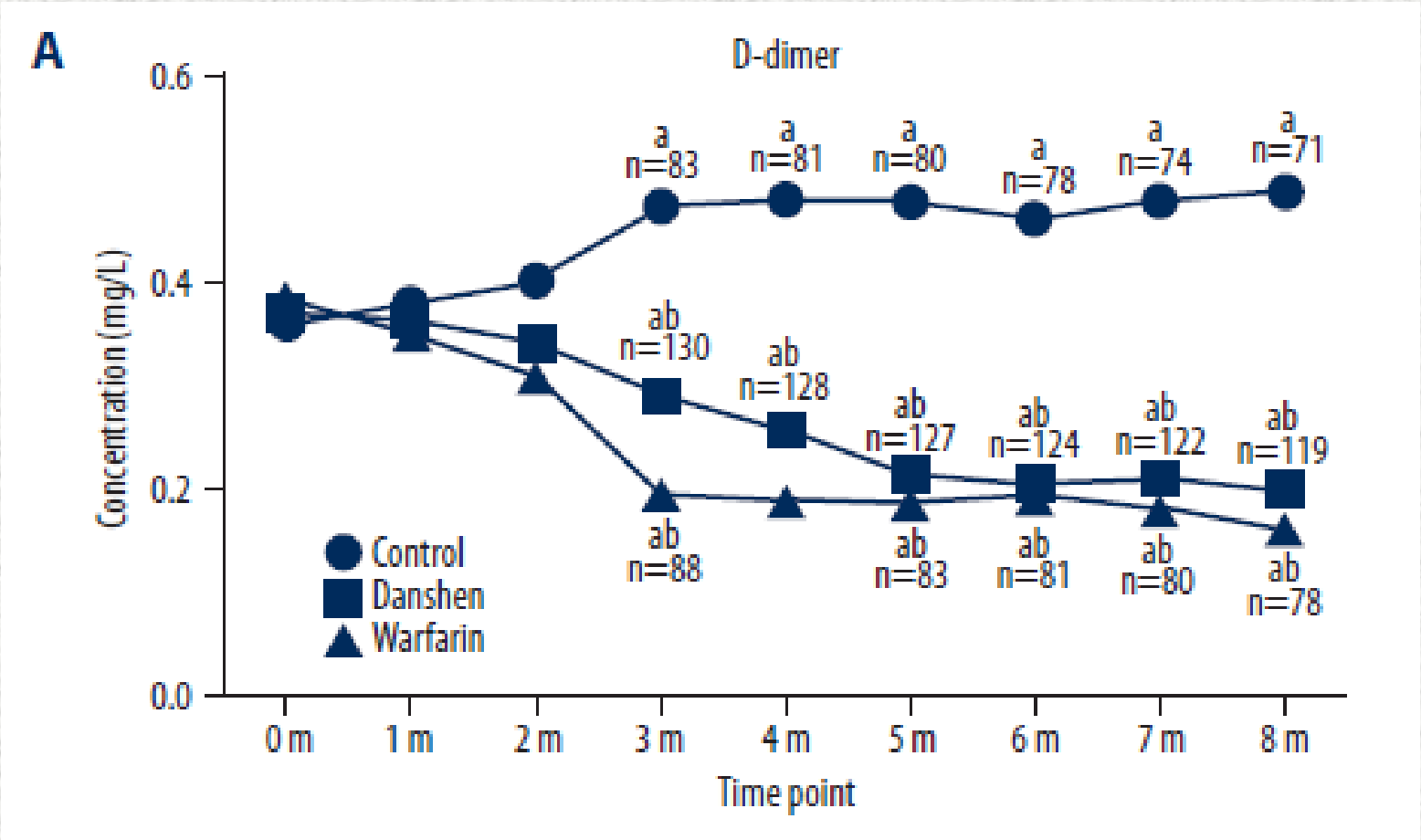
Kanama riski ≤ %3

NCT02958969

Costs distribution*	Aspirin arm	LMWH arm
Hospitalization	920,175 (67.5%)	417,331 (5.5%)
Treatment	362,164 (26.6%)	5,760,171 (75.9%)
Monitoring	79,913 (5.9%)	1,414,243 (18.6%)
Total	1,362,253 (100%)	7,591,745 (100%)
Result		
QALYs	0.300	0.299
Mean cost* (SD)	272.5 (1019)	1518.4 (601.4)
ICER		

Cost distribution and Cost effetiveness results. 2013 euros.
QALYs: quality-adjusted life years,
ICER: incremental cost effectiveness ratio

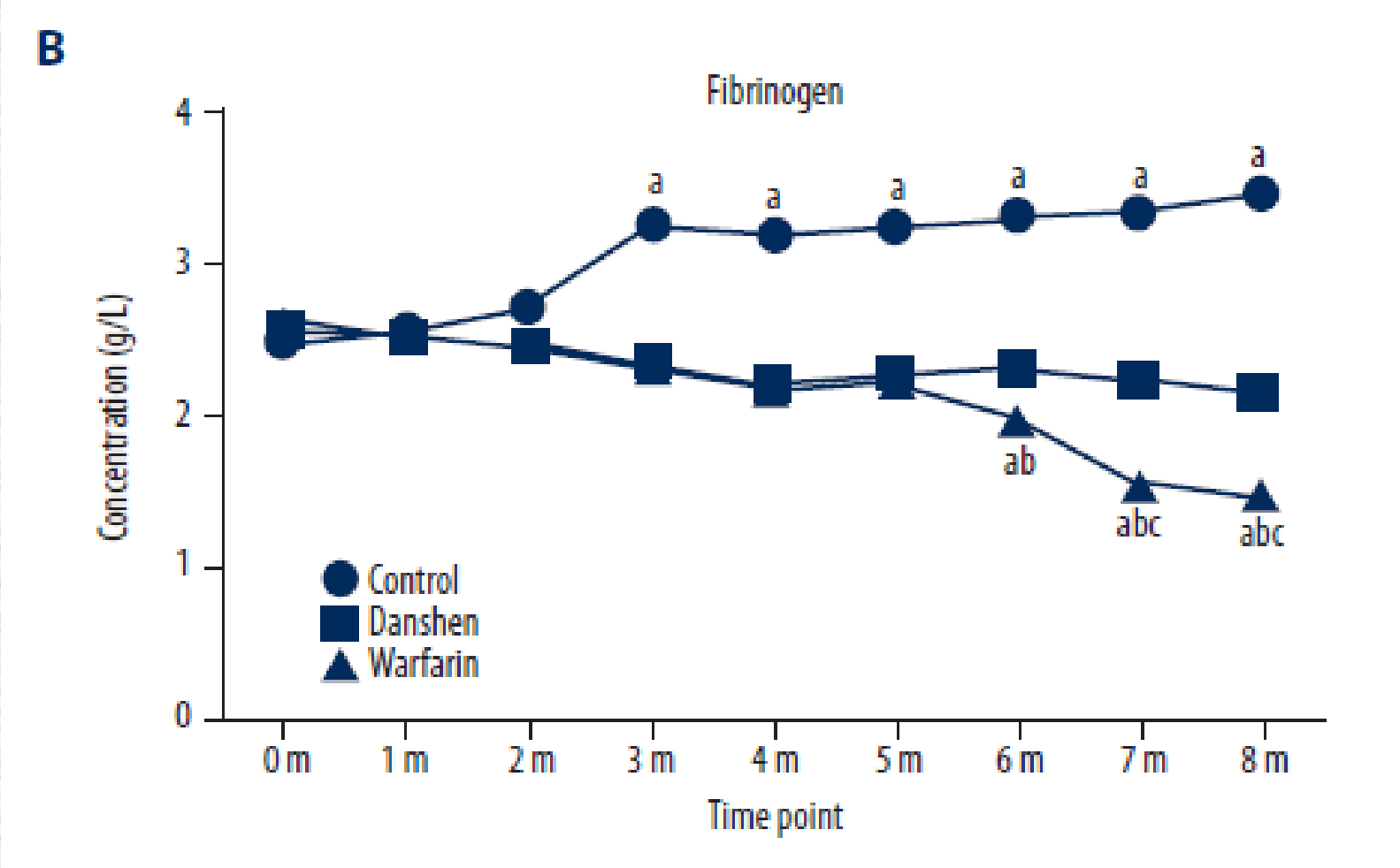
Thrombosis Research 2016; 145:119-125



Thalidomide
Hasta n= 313

Lit-21

Med Sci Monit 2016;22:3835-3842



Thalidomide
Patients n= 313

Lit-21

Med Sci Monit 2016;22:3835-3842

TEŞEKKÜRLER