Epidemiologia e clinica del tromboembolismo venoso

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Thrombophilia may present clinically as one or more of several thrombotic manifestations (“phenotypes”). The predominant clinical manifestation of thrombophilia is venous thromboembolism.

Table 1. Acquired or secondary thrombophilia.

Strongly Supportive Data
- Active cancer
- Chemotherapy (L-asparaginase, thalidomide, anti-angiogenesis therapy)
- Myeloproliferative disorders
- Heparin-induced thrombocytopenia
- Nephrotic syndrome
- Intravascular coagulation and fibrinolysis/disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Sickle cell disease
- Oral contraceptives
- Estrogen therapy
- Pregnancy/postpartum state
- Selective estrogen receptor modulator therapy (tamoxifen and raloxifene)
- Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody, anti-β2 glycoprotein-1 antibody)
- Paroxysmal nocturnal hemoglobinuria
- Wegener granulomatosis

Supportive Data
- Inflammatory bowel disease
- Thromboangiitis obliterans (Buerger disease)
- Behçet syndrome
- Varicose veins
- Systemic lupus erythematosus
- Venous vascular anomalies (e.g., Klippel Trenaunay syndrome)
- Progesterone therapy
- Infertility "therapy"
- Hyperhomocysteinemia
- HIV infection
- Dehydration

Table 2. Hereditary (familial or primary) thrombophilia.

Strongly Supportive Data
- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Activated protein C resistance
- Factor V Leiden
- Prothrombin G20210A
- Homocystinuria

Supportive Data
- Increased plasma factors I (fibrinogen), II (prothrombin), VIII, IX, XI
- Factor XIII polymorphisms
- Hyperhomocysteinemia
- Dysfibrinogenemia
- Reduced tissue factor pathway inhibitor

Weakly Supportive Data
- Reduced protein Z and Z-dependent protease inhibitor
- Tissue plasminogen activator deficiency
- Increased plasminogen activator inhibitor (PAI)-1
- Increased thrombin-activatable fibrinolysis inhibitor
- Hypoplasminogenemia and dysplasminogenemia
- Hypofibrinolysis

Heit Hematology 2007

CLINICAL MANIFESTATIONS

- purpura fulminans
- superficial or deep vein thrombosis, pulmonary embolism
- thrombosis of “unusual” venous circulations (e.g., cerebral, hepatic, mesenteric, and renal veins; possibly arm, portal and ovarian veins; not retinal vein or artery)
- Warfarin-induced skin necrosis
- possibly arterial thrombosis (e.g., stroke, acute myocardial infarction)
- recurrent fetal loss
- possibly complications of pregnancy (e.g., intrauterine growth restriction, stillbirth, severe pre-eclampsia, abruptio placentae)

COMPLICATIONS OF VTE

- VENOUS STASIS SYNDROME (POST THROMBOTIC SYNDROME)
  (76.1 per 100.000 person-years in US)

- VENOUS ULCER
  (18.0 per 100.000 person-years in US)

- CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION
  (6.5 per million person-years)

The post-thrombotic syndrome (PTS) in an important, underappreciated, chronic consequence of DVT, even when appropriate anticoagulant therapy is used.

PTS is called “syndrome” because it manifests as symptoms and clinical signs that can vary from patient to patient.

•Symptoms

intermittent or persistent

pain, heaviness, swelling, cramps, itching, or tingling in the affected limb

aggravated by standing or walking and improved by rest and leg elevation

Signs

edema

teleangiectasiae

brown pigmentation

venous eczema

secondary varicose veins

thickening of the subcutaneus tissues of the medial lower limb (lipodermatosclerosis)

leg ulcers (chronic, painful, and slow to heal and often recur)

1) VILLALTA SCALE

Binary (yes/no)
Categorical (none, mild, moderate, severe)
Continuos (range 0-33)

There is generally no need for further diagnostic investigation!!!!!

The epidemiology of Venous Thromboembolism (VTE) in the Community

- 108 per 100.000 person-years (among whites) (250.000 cases/year in USA)

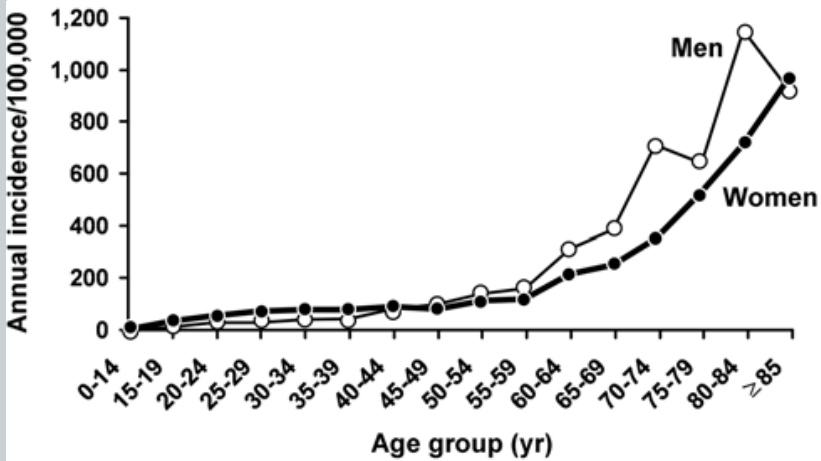
- 78 per 100.000 person-years (among black) (27.000 cases/year)

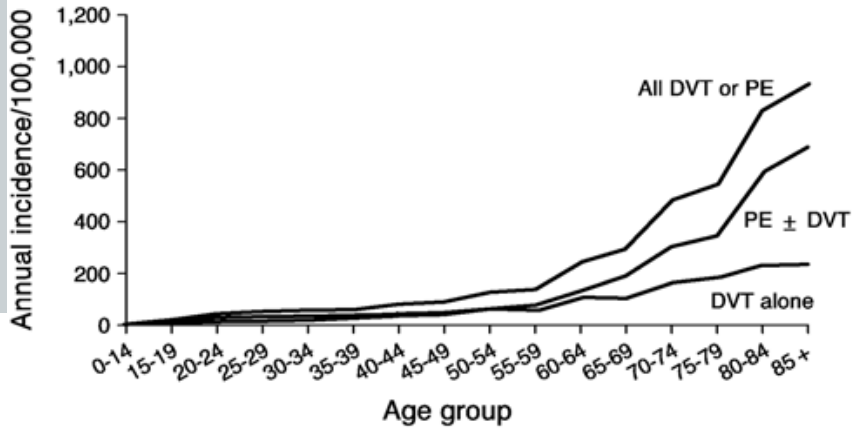
- the incidence has not changed significantly over the last 25 years

- the incidence rates increased exponentially with age for both men and women and for both deep vein thrombosis and pulmonary embolism.

- male/female sex ratio is 1.2:1 (exception during childbearing years).

- pulmonary embolism accounts for an increasing proportion of venous thromboembolism with increasing age for both genders.





Heit JA Arterioscler Thromb Vasc Biol. 2008

TABLE II. Distribution of Venous Thromboembolism Event Type by Race

Event type	White (n = 2,002)	Black (n = 395)	Total (n = 2,397)	P-value
DVT only	1,171 (58.5)	205 (51.9)	1,376 (57.4)	0.02
PE only	288 (14.4)	109 (27.6)	397 (16.6)	<0.0001
PE + DVT	543 (27.1)	81 (20.5)	624 (26.0)	0.006
DVT	1,714 (85.6)	286 (72.4)	2,000 (83.4)	<0.0001
PE	831 (41.5)	190 (48.1)	1,021 (42.6)	0.02

Heit JA et al. Am J Hematol, 2010

Characteristic	white	black	total	p value
Postsurgery	226 (11.3)	22 (5.6)	248 (10.4)	0.0006
Trauma	109 (5.4)	8 (2.0)	117 (4.9)	0.006
Cancer	216 (10.8)	45 (11.4)	261 (10.9)	0.73
Infection	51 (2.6)	2 (0.5)	53 (2.2)	0.01
HIV infection	2 (0.1)	10 (2.5)	12 (0.5)	<0.0001
Sickle cell disease	0	12 (3.0)	12 (0.5)	<0.0001
Autoimmune disease	299 (14.9)	60 (15.2)	359 (15.0)	0.90
Oral contraceptive use	156 (12.9)	17 (6.1)	173 (11.6)	0.002
Hormone therapy	35 (2.9)	2 (0.7)	37 (2.5)	0.03
Thrombophiliac	604 (30.2)	56 (14.2)	660 (27.5)	<0.0001
Family history of VTE	240 (12.0)	22 (5.6)	262 (10.9)	0.0002
Idiopathic VTE	1,381(69.0)	272 (68.9)	1,653 (69.0)	0.96
Idiopathic DVT	1,188 (59.3)	196 (49.6)	1,390 (58.0)	0.003
Idiopathic PE	580 (29.0)	135 (34.2)	715 (29.8)	0.04

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Characteristic	White (n = 2,002)	Black (n = 395)	Total (n = 2,397)	P-value
Stroke	104 (5.2)	25 (6.3)	129 (5.4)	0.36
Cerebral palsy	2 (0.1)	0	2 (0.1)	1.0
Coronary artery disease	97 (4.9)	24 (6.1)	121 (5.1)	0.31
Congenital heart disease	14 (0.7)	4 (1.0)	18 (0.8)	0.52
Prosthetic heart valve	8 (0.4)	7 (1.8)	15 (0.6)	0.006
Congestive heart failure	26 (1.3)	8 (2.0)	34 (1.4)	0.26
Peripheral artery disease	26 (1.3)	5 (1.3)	31 (1.3)	1.0
Hypertension	398 (19.9)	150 (38.0)	548 (22.9)	<0.0001
Hyperlipidemia	282 (14.1)	50 (12.7)	332 (13.9)	0.45
Diabetes mellitus	136 (6.8)	54 (13.7)	190 (7.9)	<0.0001
Liver disease	22 (1.1)	8 (2.0)	30 (1.3)	0.14
Renal disease	71 (3.6)	30 (7.6)	101 (4.2)	0.0003
Dialysis	14 (0.7)	10 (2.5)	24 (1.0)	0.003

Distribution of venous thromboembolism risk factors by race and gender

Characteristic	Female			Male		
	White (n = 1,214)	Black (n = 279)	P-value	White (n = 788)	Black (n = 116)	P-value
Postsurgery	140 (11.5)	13 (4.7)	0.0006	86 (10.9)	9 (7.8)	0.30
Trauma	55 (4.5)	3 (1.1)	0.007	54 (6.9)	5 (4.3)	0.30
Cancer	123 (10.1)	26 (9.3)	0.68	93 (11.8)	19 (16.4)	0.16
Infection	33 (2.7)	1 (0.4)	0.02	18 (2.3)	1 (0.9)	0.50
HIV infection	1 (0.1)	6 (2.2)	0.0002	1 (0.1)	3 (3.5)	0.0012
Autoimmune disease	217 (17.9)	47 (16.9)	0.68	82 (10.4)	13 (11.2)	0.79
Sickle cell disease	0	10 (3.6)	<0.0001	0	2 (1.7)	0.02
Idiopathic VTE	774 (63.8)	184 (66.0)	0.50	607 (77.0)	88 (75.9)	0.78
Idiopathic DVT	659 (54.3)	130 (46.6)	0.02	529 (67.1)	72 (62.1)	0.28
Idiopathic PE	298 (24.6)	88 (31.5)	0.02	282 (35.8)	47 (40.5)	0.32

Independent RISK FACTORS for deep vein thrombosis or pulmonary embolism

GENETICS ⟷ **ACQUIRED**

Baseline characteristic	Odds ratio	95% CI
Hospitalization		
Hospitalization for acute medical illness	7.98	4.49,14.18
Hospitalization for major surgery	21.72	9.44, 49.93
Trauma	12.69	4.06, 39.66
Active cancer without chemotherapy	4.05	1.93, 8.52
Active cancer with chemotherapy	6.53	2.11, 20.23
Prior central venous catheter or transvenous pacemaker	5.55	1.57, 19.58
Prior superficial vein thrombosis	4.32	1.76, 10.61
Neurologic disease with extremity paresis	3.04	1.25, 7.38
Serious liver disease	**0.10**	**0.01, 0.71**

Heit JA et al. Arch Intern Med, 2000

ORIGINAL ARTICLE

Rates of venous thromboembolism in multiple myeloma patients undergoing immunomodulatory therapy with thalidomide or lenalidomide: a systematic review and meta-analysis

M. CARRIER,* G. LE GAL,† J. TAY,‡ C. WU§ and A. Y. LEE¶

Table 6 Rate of venous thromboembolism (per 100 patient-months) in patients with previously treated multiple myeloma managed with thalidomide-based regimens

	No prophylaxis	ASA	Warfarin 1–1.25 mg per day	Prophylactic LMWH	Therapeutic doses of anticoagulation*
Thalidomide alone (95% CI)	0.4 (0.2–0.8) (n = 706)			0 (0–1.72) (n = 17)	
Thalidomide + prednisone (95% CI)	0.6 (0.2–1.1) (n = 258)				
Thalidomide + other chemotherapy agents (95% CI)	0.4 (0.01–1.2) (n = 38)	0.4 (0.01–0.9) (n = 37)			
Thalidomide + dexamethasone (95% CI)	0.8 (0.1–2.1) (n = 321)	†			
Thalidomide + dexamethasone + other chemotherapy agents (95% CI)	0.9 (0.3–1.8) (n = 321)		2.4 (1.3–4.0) (n = 102)		0 (0–2.2) (n = 18)
Thalidomide + dexamethasone + multi-agent chemotherapy including doxorubicin (95% CI)	6.7 (0.5–18.9) (n = 331)		3.5 (1.2–6.5) (n = 50)		

*Therapeutic doses of anticoagulation: (i) warfarin with target INR between 2.0 and 3.0 or (ii) therapeutic doses of low-molecular-weight heparin. †Only one study reported subgroups of patients with ASA thromboprophylaxis started at the initiation of (n = 58) or during (n = 26) the study protocol. CI, confidence intervals; LMWH, low-molecular-weight heparin; n, total number of patients.

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Guideline: Recommendations for Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer

Gary H. Lyman, Alok A. Khorana, Anna Falanga, Daniel Clarke-Pearson, Christopher Flowers,

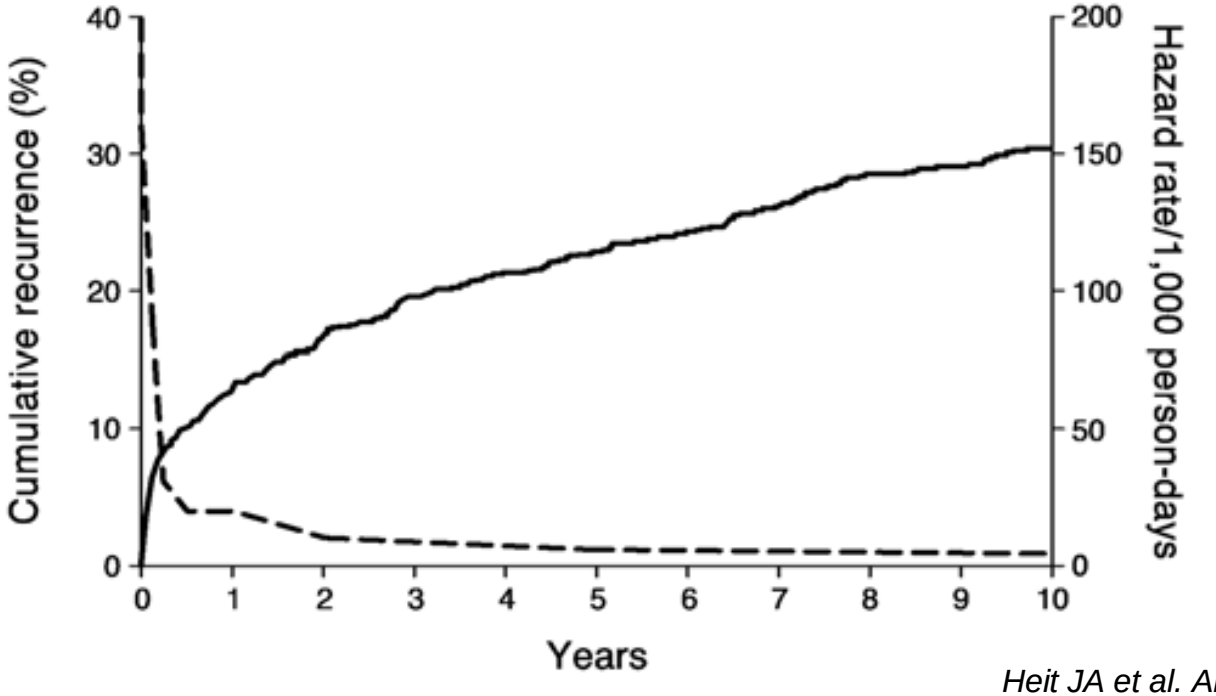
Table 1. Risk Factors for VTE in Patients With Malignant Disease

Patient-related factors
Older age[15]
Race (higher in African Americans; lower in Asian-Pacific Islanders)[20]
Comorbid conditions (obesity, infection, renal disease, pulmonary disease, arterial thromboembolism)[15,21,26,33]
Prior history of VTE[26]
Elevated prechemotherapy platelet count[21]
Heritable prothrombotic mutations[19,34-36]
Cancer-related factors
Primary site of cancer (GI, brain, lung, gynecologic, renal, hematologic)[9,15,19-21,23]
Initial 3-6 months after diagnosis[19,20,33]
Current metastatic disease[15,19,20,23,33,37]
Treatment-related factors
Recent major surgery[32,38,39]
Current hospitalization[15,26,40]
Active chemotherapy[2,23,26,37]
Active hormonal therapy[37,41-43]
Current or recent antiangiogenic therapy (thalidomide, lenalidomide, bevacizumab*)[11,28-31,44-46]
Current erythropoiesis-stimulating agents[21,24]
Presence of central venous catheters[32,47-49]

Abbreviation: VTE, venous thromboembolism.
*Bevacizumab is clearly associated with an increased risk of arterial thrombotic events; an association with venous thrombosis is not fully established.

Independent predictors of venous thromboemobolism recurrence

Characteristic	Hazard ratio	95% CI
Age*	1.17	1.11, 1.24
Body mass index†	1.24	1.04, 1.47
Neurologic disease with extremity paresis	1.87	1.28, 2.73
Active cancer		
With chemotherapy	4.24	2.58, 6.95
Without chemotherapy	2.21	1.60, 3.06



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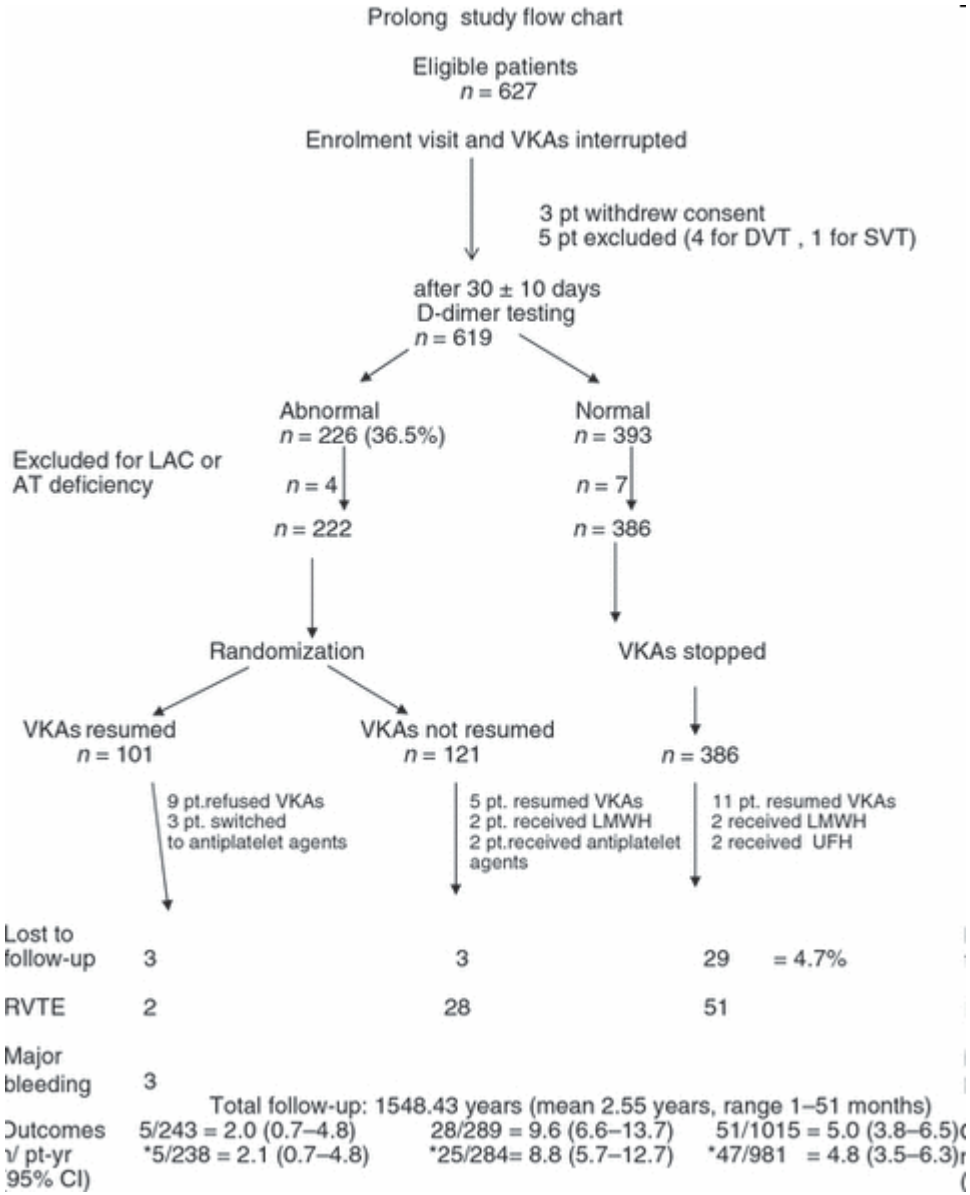
PROLONG STUDY



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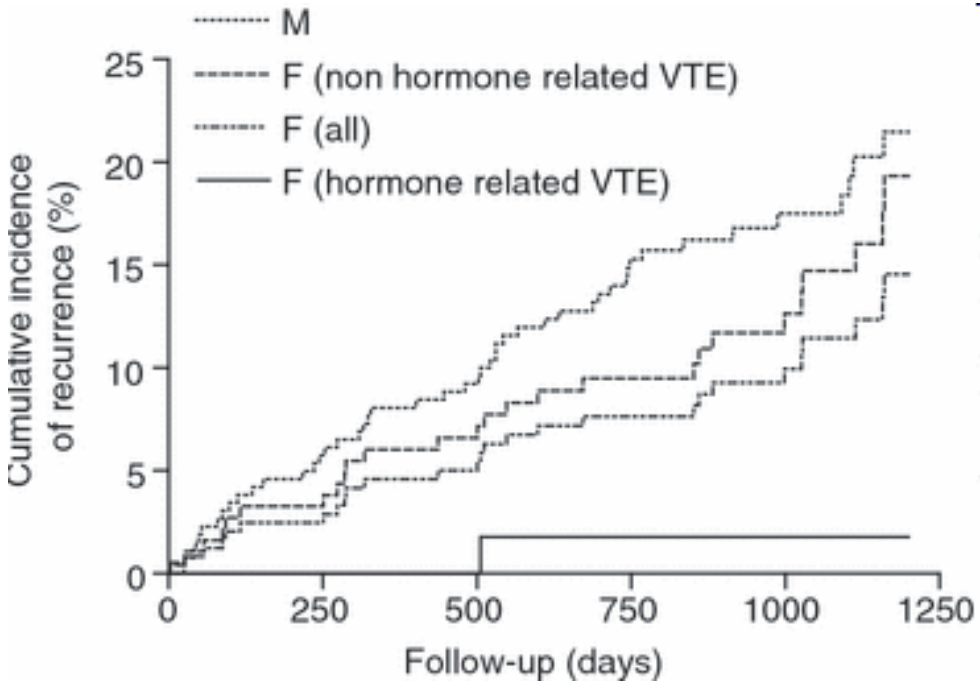
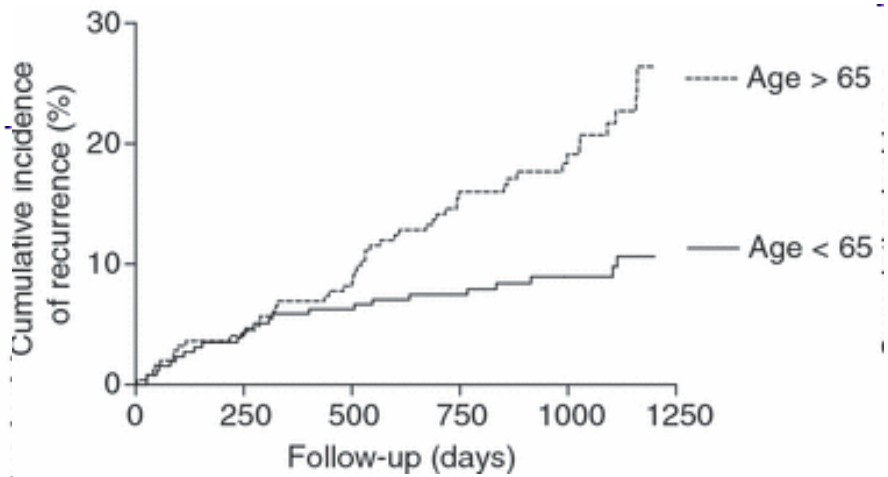
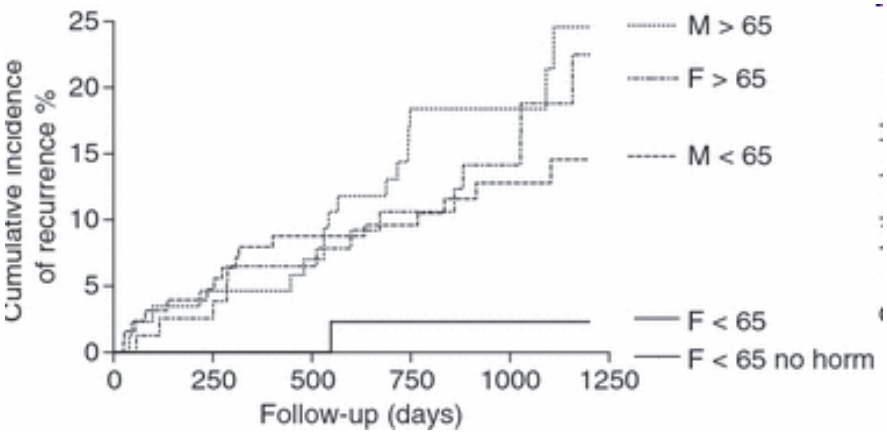
Cumulative incidence of main outcomes according to sex and age







Cumulative incidence of main outcomes in subjects with normal D-Dimer according to sex and age

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