Venous thromboembolism after stroke:
Does race matter?

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Departments of Medicine, Oncology and Epidemiology and Biostatistics
Western University

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Disclosures

Dr. Alejandro Lazo-Langner

Advisory board or similar committee	Pfizer, Leo Pharma
Clinical trials or studies	Pfizer, Bayer, Leo Pharma, Daiichi Sankyo, Novartis, Celgene
Honoraria or other fees	Pfizer, Leo Pharma, Boehringer Ingelheim
Research grants	Alexion Pharmaceuticals, Canadian Institutes for Health Research, Heart and Stroke Foundation, Ministry of Health and Long Term Care, AMOSO Foundation, CanVECTOR group

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Agenda

- Why do clots matter?
  - Overview of VTE
- What is the incidence of VTE in stroke patients?
  - Epidemiology of VTE after stroke
- How do we prevent VTE in stroke patients?
  - Is anticoagulant prophylaxis effective?
  - Is anticoagulant prophylaxis safe?

3

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Why do clots matter?

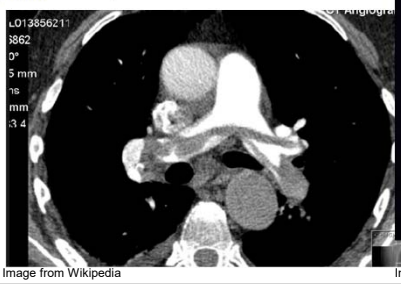

Image from Wikipedia

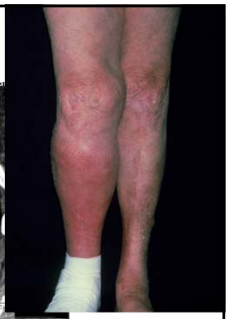

Image from Stubbs et al BMJ 2018

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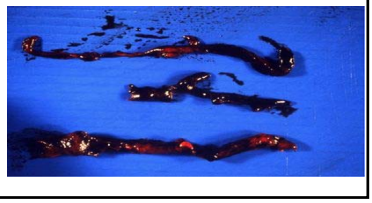

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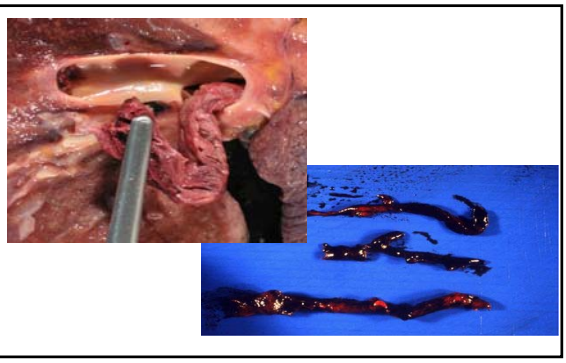

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Why do clots matter?

- Venous thromboembolism
  - Third vascular cause of mortality
  - 200,000 cases per year in Canada
  - 60,000 hospitalizations

Lazo-Langner A, et al. Res Pract Thromb Haemost 2018

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Why do clots matter?

Thrombosis Compendium

Global Burden of Thrombosis

Epidemiologic Aspects

Aaron M. Wendelboe, Gary E. Raskob

Table. Incidence, Mortality, YLD, and DALY Estimates of Thrombotic Conditions per 100 000 Population

Measure	Ischemic Heart Disease*	Ischemic Stroke*	Atrial Fibrillation*	Venous Thromboembolism
Incidence	1518.7 (2013)	114.3 (2013)	77.5 males (2010), 59.5 females (2010)	115–269 (2010)†
Mortality	105.5 (2010)	42.3 (2010)	1.7 (2010)	9.4–32.3 (1998–2008)[15,16]
YLDs	5.8 (2013)	2.7 (2013)	0.9 (2013)	Not available
DALY	654–2855 (2010)[17]	217–1361 (2010)[18]	45.9–64.5 (2010)	Not available†

DALY indicates disability-adjusted life-year; and YLD, years lived with disability.
*Estimates from the Global Burden of Disease project.[3,11,12]
†A single study estimated hospital-associated DALYs of pulmonary embolism to be 7.6.[18]

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Why do clots matter?

Thrombosis Compendium

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Epidemiologic Aspect

Aaron M. Wood[illegible] Gary [illegible]askob

Table. Incidence, Mortality, YLD, and [illegible] of Thrombotic Conditions per 100 000 Population

Measure	Ischemic [illegible]	Ischemic Stroke*	Atrial Fibrillation*	Venous Thromboembolism
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Circulation Research April 29, 2016

Clots kill people!

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Clots kill people

Causes of Death in U.S.	Deaths/Yr
AMI	215,000
Pulmonary Embolism	200,000
Accidents	97,835
Highway Fatalities	41,800
Breast Cancer	40,200
AIDS	13,426

Total < PE

2002 AHA Heart and Stroke Update.
Heit J, et al. Blood. 2005;106.
Anderson FA Jr, et al. Am J Hematol. 2007;82.

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Clots kill people

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Accidents	97,835
Highway Fatalities	41,800
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AIDS	13,426

Studies in the US
7% treated unsuccessfully, 34% sudden and fatal, and 59% undetected

Total < PE

2002 AHA Heart and Stroke Update.
Heit J, et al. Blood. 2005;106.
Anderson FA Jr, et al. Am J Hematol. 2007;82.

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Clots are frequent

- Incidence in Ontario
  - VTE 125 per 100,000 PY (95% CI 123 to 127)
  - DVT 97 per 100,000 PY (95% CI 96 to 99)
  - PE 36 per 100,000 PY (95% CI 35 to 37)

Lazo-Langner A, et al. Res Pract Thromb Haemost 2018

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Does race matter?

- Systematic review
- VTE incidence per 100,000 PY
  - 162 and 439 in Caucasians
  - 143 and 746 in Africans
  - 3.2 and 16.6 in Asians
  - 13.9 and 94 in Hispanics
  - Hospital incidence of VTE per 100,000 PY
    - 21 and 131 in Caucasians
    - 22 and 155 in Africans
    - 2 and 26 in Asians
    - 33.1 and 71 in American Indians/Alaskan Indians
    - 9 in Hispanics.

Al-Ani et al. Blood 2015

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Yes, race does matter

Received: 22 February 2018 | Accepted: 23 April 2018
DOI: 10.1002/rth2.12113

ORIGINAL ARTICLE

rpth

Immigration, region of origin, and the epidemiology of venous thromboembolism: A population-based study

Alejandro Lazo-Langner MD, MSc[1,2,3] | Kuan Liu MSc[3] | Salimah Shariff PhD[3] | Amit X. Garg MD, PhD, FRCPC[2,3,4] | Joel G. Ray MD, MSc, FRCPC[5,6]

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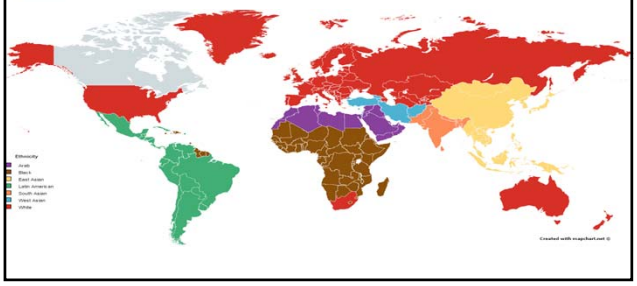
Ethnicity distribution



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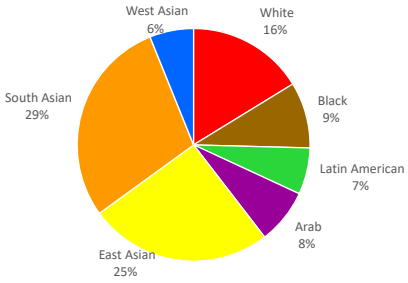
Results - Population Characteristics



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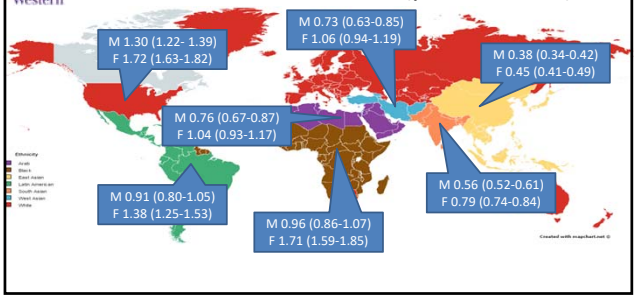
Results – Incidence rates (per 1,000 PY)



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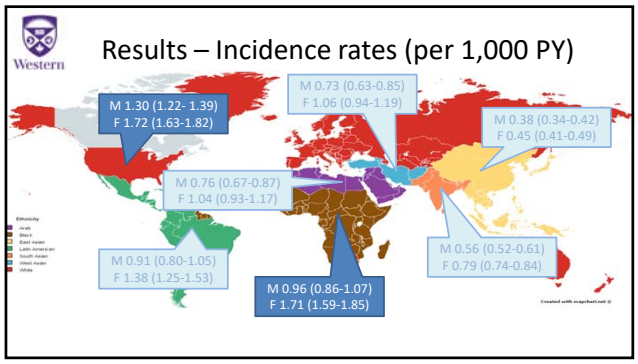
Western
Results – Incidence rates (per 1,000 PY)
M 1.30 (1.22- 1.39)
F 1.72 (1.63-1.82)
M 0.73 (0.63-0.85)
F 1.06 (0.94-1.19)
M 0.38 (0.34-0.42)
F 0.45 (0.41-0.49)
M 0.76 (0.67-0.87)
F 1.04 (0.93-1.17)
M 0.56 (0.52-0.61)
F 0.79 (0.74-0.84)
M 0.91 (0.80-1.05)
F 1.38 (1.25-1.53)
M 0.96 (0.86-1.07)
F 1.71 (1.59-1.85)

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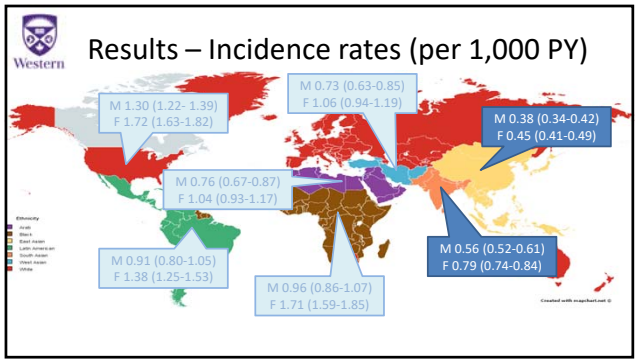
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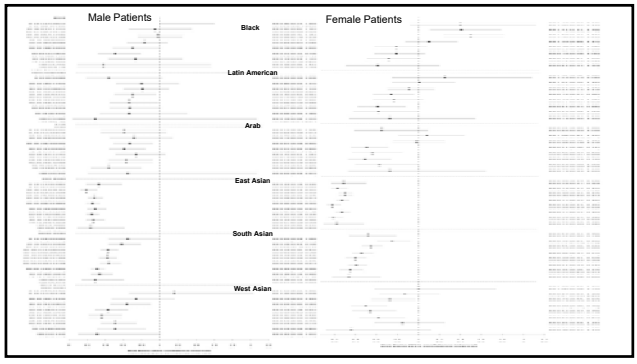
Male Patients
Female Patients
Black
Latin American
Arab
East Asian
South Asian
West Asian

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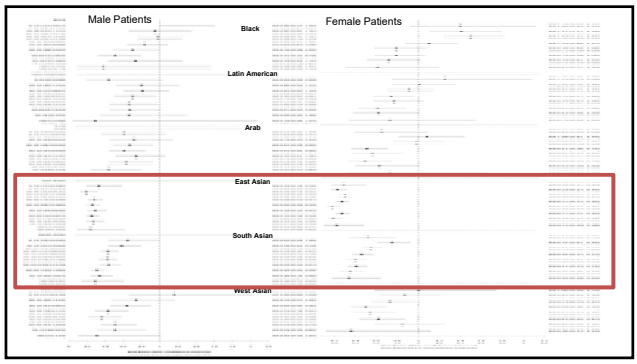
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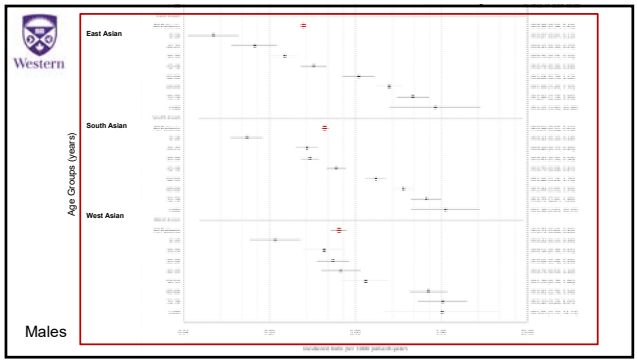
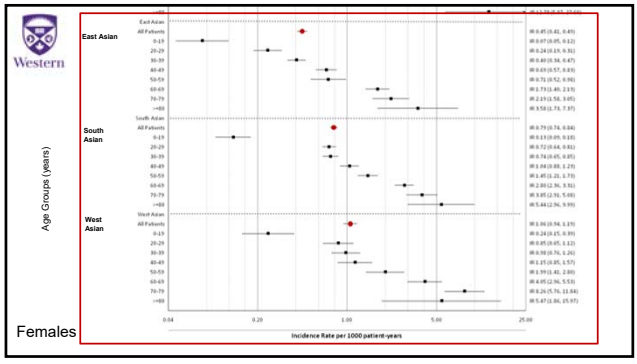
22


Western
East Asian
South Asian
West Asian
Age Groups (years)
Males

23


Western
East Asian
South Asian
West Asian
Age Groups (years)
Females
Incidence Rate per 1000 patient-years

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Review Article 2243

Incidence of Venous Thromboembolism in Asian Populations: A Systematic Review

Lai Heng Lee[1,2,3] Alexander Gallus[4,5] Ravul Jindal[6] Chen Wang[7,8] Chau-Chung Wu[9,10]

Thromb Haemost 2017;117:2243–2260.

- Increasing incidence of VTE
  - Korea
  - Japan
  - China
  - Singapore

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Pulmonary Embolism Incidence and Fatality Trends in Chinese Hospitals from 1997 to 2008: A Multicenter Registration Study

Yuanhua Yang[1,2*], Lirong Liang[1,2*], Zhenguo Zhai[1,2], Hangyong He[1,2], Wanmu Xie[1,2], Xiaoxia Peng[3,4], Chen Wang[1,2,5], on behalf of investigators for the National Cooperative Project for the Prevention and Treatment of PTE-DVT

November 2011 | Volume 6 | Issue 11 | e26861

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Pulmonary Embolism Incidence and Fatality Trends in

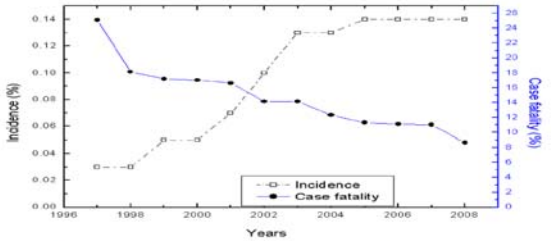

Figure 1. Incidence and case fatality rates for PE in hospitalized adults from 1997 to 2008.
doi:10.1371/journal.pone.0026861.g001

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In summary…

- Overall VTE is frequent worldwide
- High mortality
- Incidence of VTE in Asia is lower
  - Higher incidence in elderly
- Incidence is raising

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  - Is anticoagulant prophylaxis safe?

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VTE in stroke

Study	No. of pts.	% DVT	% PE	% Fatal PE
Warlow 1972	30	60	13	25
Denham 1973	47	46.8	---	---
Warlow 1976 a	76	53	15.8	71
Warlow 1976 b	15	53	---	---
Gibberd 1976	26	50	3.8	0
McCarthy 1977	16	75	---	---
Miyamoto 1980	141	29	0 (Tx.)	0
Bounds 1981	100	---	13	---
McCarthy 1986	161	72.2	19.8	100
Turpie 1987	25	28	8	0
Bornstein 1988	49	22.5	2	0
Scmidt 1988	1538	---	7.1 (13.6/5.2)	---
Landi 1992	70	28.6	11.4	40

Hamilton et al. Neurosurgery 1994.

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Hamilton et al. Neurosurgery 1994.

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VTE in stroke

- CAST
  - 21,106 pts.
  - 4 weeks of ASA
  - Death, dependence, recurrence
  - Clinical diagnosis
- IST
  - 19,435 pts.
  - 3 x 2 factorial
  - UFH (Hi-Low-No) ASA
  - Death @ 14 d, death or dependency @ 6 mo

	Aspirin N (%)	**Placebo N (%)**
Total PE	12 (0.1)	**20 (0.2)**
Fatal PE	5 (0.1)	**10 (0.1)**

	Heparin N (%)	**No Heparin N (%)**
Total PE	53 (0.5)	**81 (0.8)**
Fatal PE	36 (0.4)	**39 (0.4)**

CAST Collaborative Group. Lancet 1997.
International Stroke Trial Collaborative Group. Lancet 1997.

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CAST Collaborative Group. Lancet 1997.
International Stroke Trial Collaborative Group. Lancet 1997

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VTE in stroke

Outcomes at 4 weeks!

Outcomes at 2 weeks!

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Venous Thromboembolism in Patients With Ischemic and Hemorrhagic Stroke

Elias Skaf, MD[a], Paul D. Stein, MD[a,b,*], Afzal Beemath, MD[a], Julia Sanchez, MD[a], Mark A. Bustamante, MD[a], and Ronald E. Olson, PhD[c]

Am J Cardiol 2005;96:1731–1733

- National Hospital Discharge Survey
  - 1979-2003
  - Ischemic stroke >14,000,000 patients
  - Hemorrhagic stroke >1,600,000 patients

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Western

Venous *Thromboembolism in Patients With Ischemic and Hemorrhagic Stroke*

Elias S

- Nationa
  - 1979-
  - Ische
  - Hemo

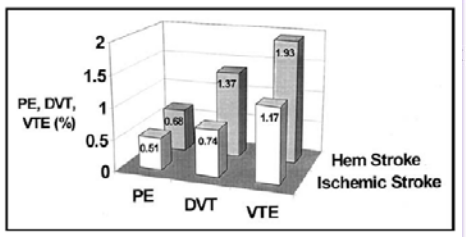

Figure 1. Rates of PE, DVT, and VTE in hospitalized patients with ischemic and hemorrhagic (Hem) stroke. Data were averaged from 1979 to 2003.

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ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Ischemic Stroke and Risk of Venous Thromboembolism in the General Population: The Tromsø Study

Ludvig B. Rinde, BSc; Birgit Småbrekke, BCs; Ellisiv B. Mathiesen, MD, PhD; Maja-Lisa Løchen, MD, PhD; Inger Njølstad, MD, PhD; Erin M. Hald, MD, PhD; Tom Wilsgaard, PhD; Sigrid K. Brækkan, PhD; John-Bjarne Hansen, MD, PhD

J Am Heart Assoc. 2016;5:e004311

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Table 3. Incidence Rates and Hazard Ratios for VTE, DVT, and PE According to Ischemic Stroke Exposure

	Person-Years	VTE Events	Crude IR (95% CI)*	Model 1[†] HR (95% CI)	Model 2[‡] HR (95% CI)	Model 3[§] HR (95% CI)
Total VTE						
No stroke	361 634	665	1.8 (1.7–2.0)	Reference	Reference	Reference
<1 month	122	10	82.1 (44.2–152.5)	16.4 (8.7–30.8)	15.8 (8.4–29.8)	19.7 (10.1–38.5)
1 to 3 months	172	8	46.5 (23.2–92.9)	9.5 (4.7–19.2)	9.2 (4.5–18.5)	10.6 (5.0–22.5)
>3 months	5193	39	7.5 (5.5–10.3)	1.5 (1.1–2.1)	1.4 (1.0–2.0)	1.5 (1.1–2.2)
DVT						
No stroke	361 634	386	1.1 (1.0–1.2)	Reference	Reference	Reference
<1 month	122	6	49.2 (22.1–109.6)	17.7 (7.8–39.9)	17.4 (7.7–39.2)	19.1 (7.8–46.9)
1 to 3 months	172	4	23.2 (8.7–61.9)	8.7 (3.2–23.4)	8.5 (3.1–22.9)	10.3 (3.8–28.0)
>3 months	5193	19	3.7 (2.3–5.7)	1.3 (0.8–2.1)	1.2 (0.8–2.0)	1.3 (0.8–2.3)
PE						
No stroke	361 634	279	0.8 (0.7–0.9)	Reference	Reference	Reference
<1 month	122	4	32.8 (12.3–87.5)	14.8 (5.5–40.0)	14.0 (5.2–37.0)	20.2 (7.4–55.1)
1 to 3 months	172	4	23.2 (8.7–61.9)	10.4 (3.9–28.3)	10.0 (3.7–27.1)	11.2 (3.5–35.5)
>3 months	5193	20	3.9 (2.5–6.0)	1.7 (1.1–2.7)	1.6 (1.0–2.5)	1.8 (1.0–3.0)

The Tromsø Study 1994–2010. DVT indicates deep vein thrombosis; HR, hazard ratio; IR, incidence rates; PE, pulmonary embolism; VTE, venous thromboembolism.
*Per 1000 persons-years.
†Model 1: Age as timescale, adjusted for sex.
‡Model 2: Model 1+body mass index.
§Model 3: Model 2+systolic blood pressure, diabetes mellitus, high-density lipoprotein cholesterol, smoking, physical activity, and education level.

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>3 months	5193	19	3.7 (2.3–5.7)	1.3 (0.8–2.1)	1.2 (0.8–2.0)	1.3 (0.8–2.3)
PE						
No stroke	361 634	279	0.8 (0.7–0.9)	Reference	Reference	Reference
<1 month	122	4	32.8 (12.3–87.5)	14.8 (5.5–40.0)	14.0 (5.2–37.0)	20.2 (7.4–55.1)
1 to 3 months	172	4	23.2 (8.7–61.9)	10.4 (3.9–28.3)	10.0 (3.7–27.1)	11.2 (3.5–35.5)
>3 months	5193	20	3.9 (2.5–6.0)	1.7 (1.1–2.7)	1.6 (1.0–2.5)	1.8 (1.0–3.0)

The Tromsø Study 1994–2010. DVT indicates deep vein thrombosis; HR, hazard ratio; IR, incidence rates; PE, pulmonary embolism; VTE, venous thromboembolism.
*Per 1000 persons-years.
†Model 1: Age as timescale, adjusted for sex.
‡Model 2: Model 1+body mass index.
§Model 3: Model 2+systolic blood pressure, diabetes mellitus, high-density lipoprotein cholesterol, smoking, physical activity, and education level.

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Table 3. Incidence Rates and Hazard Ratios for VTE, DVT, and PE According to Ischemic Stroke Exposure

	Person-Years	VTE Events	Crude IR (95% CI)*	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)	Model 3§ HR (95% CI)
Total VTE						
No stroke	361 634	665	1.8 (1.7–2.0)	Reference	Reference	Reference
<1 month	122	10	82.1 (44.2–152.5)	16.4 (8.7–30.8)	15.8 (8.4–29.8)	19.7 (10.1–38.5)
1 to 3 months	172	8	46.5 (23.2–92.9)	9.5 (4.7–19.2)	9.2 (4.5–18.5)	10.6 (5.0–22.5)
>3 months	5193	39	7.5 (5.5–10.3)	1.5 (1.1–2.1)	1.4 (1.0–2.0)	1.5 (1.1–2.2)
DVT						
No stroke	361 634	386	1.1 (1.0–1.2)	Reference	Reference	Reference
<1 month	122	6	49.2 (22.1–109.6)	17.7 (7.8–39.9)	17.4 (7.7–39.2)	19.1 (7.8–46.9)
1 to 3 months	172	4	23.2 (8.7–61.9)	8.7 (3.2–23.4)	8.5 (3.1–22.9)	10.3 (3.8–28.0)
>3 months	5193	19	3.7 (2.3–5.7)	1.3 (0.8–2.1)	1.2 (0.8–2.0)	1.3 (0.8–2.3)
PE						
No stroke	361 634	279	0.8 (0.7–0.9)	Reference	Reference	Reference
<1 month	122	4	32.8 (12.3–87.5)	14.8 (5.5–40.0)	14.0 (5.2–37.0)	20.2 (7.4–55.1)
1 to 3 months	172	4	23.2 (8.7–61.9)	10.4 (3.9–28.3)	10.0 (3.7–27.1)	11.2 (3.5–35.5)
>3 months	5193	20	3.9 (2.5–6.0)	1.7 (1.1–2.7)	1.6 (1.0–2.5)	1.8 (1.0–3.0)

The Tromsø Study 1994–2010. DVT indicates deep vein thrombosis; HR, hazard ratio; IR, incidence rates; PE, pulmonary embolism; VTE, venous thromboembolism.
*Per 1000 persons-years.
†Model 1: Age as timescale, adjusted for sex.
‡Model 2: Model 1+body mass index.
§Model 3: Model 2+systolic blood pressure, diabetes mellitus, high-density lipoprotein cholesterol, smoking, physical activity, and education level.

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Western

Symptomatic Pulmonary Embolism Among Stroke Patients in Taiwan: A Retrospective Cohort Study

Chih-Chi Chen, MD,[1] Tsong-Hai Lee, MD, PhD,[2] Chia-Ying Chang, MD,[1] Wei-Han Chang, MD,[1] Jia-Pei Hong, MD,[1] Li-Ting Huang, MD,[1] Simon F.T. Tang, MD,[1] and Chih-Kuang Chen, MD[1]

[1]Department of Physical Medicine and Rehabilitation, [2]Department of Neurology, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan

Topics in Stroke Rehabilitation/Sept-Oct 2012

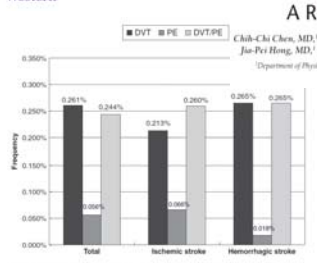

Figure 3. Frequency of symptomatic deep venous thrombosis (DVT) and/or pulmonary embolism (PE) in stroke patients.

Outcomes at hospital discharge

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High incidence of symptomatic venous thromboembolism in Thai hospitalized medical patients without thromboprophylaxis

Satimai Aniwan and Ponlapat Rojnuckarin

Blood Coagulation and Fibrinolysis 2010, 21:334–338

- Prospective cohort
  - June 2007 – December 2008
  - King Chulalongkorn Memorial Hospital
  - No prophylaxis

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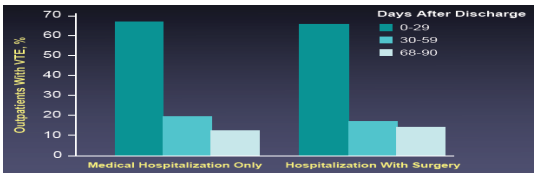
The risk does not end at discharge



- 74% of VTEs present in outpatients
- 23% of outpatient VTE patients have had recent surgery; 37% recently hospitalized
- Only 43% had received VTE prophylaxis

Spencer FA, et al. *Arch Intern Med. 2007;167:1471-1475*

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In summary…

- VTE risk after stroke is high
  - HR 10-20 during the first 3 months
  - Confirmed in multiple settings
    - Europe
    - Americas
    - Asia

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Agenda

- Why do clots matter?
  - Overview of VTE
- What is the incidence of VTE in stroke patients?
  - Epidemiology of VTE after stroke
- How do we prevent VTE in stroke patients?
  - Is anticoagulant prophylaxis effective?
  - Is anticoagulant prophylaxis safe?

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Many patients are at risk

- Annual number at risk for VTE:
  - US hospitals:
    - 7.7 million medical service inpatients
    - 4.3 million surgical service inpatients
    - 2/3 of VTE cases and deaths are hospital-acquired

1. Heit J, et al. *Blood. 2005;106:Abstract 910.*
2. Anderson FA Jr, et al. *Am J Hematol. 2007;82:777-782.*

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Independent risk factors for 1st lifetime VTE – Olmstead County

RISK FACTOR[a]	AR[b]	95% CI
Hospitalization or nursing home	58.8	53.4-64.2
Hospitalization with surgery	23.8	20.3-27.3
Hospitalization without surgery	21.5	17.3-25.6
Nursing home	13.3	9.9-16.8
Active malignant neoplasm	18.0	13.4-22.6
Trauma	12.0	9.0-14.9
Congestive heart failure	9.5	3.3-15.8
Prior central venous catheter or pacemaker	9.1	5.7-12.6
Neurological disease with extremity paresis	6.9	3.5-10.2
Prior superficial vein thrombosis	5.4	3.0-7.7

[a]All 8 risk factors together accounted for 74% of all observed VTE cases.
[b]All values are given as percentages. AR = attributable risk. Adjusted for age, sex, year, and terms in final model.

Heit JA, et al. *Arch Intern Med.* 2002;162:1245-1248.

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Independent risk factors for 1st lifetime VTE – Olmstead County

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[a]All 8 risk factors together accounted for 74% of all observed VTE cases.
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Heit JA, et al. *Arch Intern Med*. 2002;162:1245-1248.

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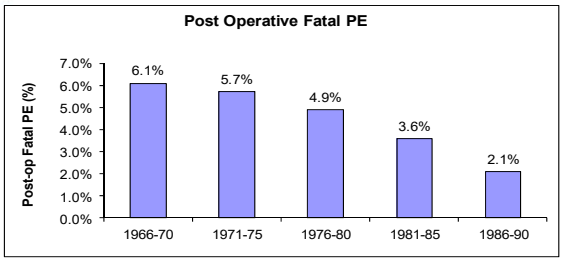
Better Prevention = Fewer Post-Operative PE



Cohen et al. Haemostasis 1996; 26:65-71

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Prophylaxis in hospitalized patients

	% Ca. patients	Proximal DVT Symptomatic VTE	RR 95% CI
MEDENOX	12.4%	Enoxaparin 2.1% Placebo 6.6% P=0.037	0.37 0.22 – 0.63
PREVENT	5.1%	Dalteparin 2.6% Placebo 5.0% P=0.002	0.55 0.38 – 0.8
ARTEMIS	15.4%	Fondaparinux 1.5% Placebo 3.4% P=0.085	0.47 0.08 – 0.69

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Western

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Prevention of VTE in Nonsurgical Patients

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Susan R. Kahn, MD; Wendy Lim, MD; Andrew S. Dunn, MD; Mary Cushman, MD; Francesco Dentali, MD; Elie A. Akl, MD, MPH, PhD; Deborah J. Cook, MD, MSc(Epi); Alex A. Balekian, MD, MSHS; Russell C. Klein, MD; Huong Le, MD, FCCP; Sam Schulman, MD; and M. Hassan Murad, MD, MPH

CHEST / 141 / 2 / FEBRUARY, 2012 SUPPLEMENT

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2.3. For acutely ill hospitalized medical patients at increased risk of thrombosis (Table 2), we recommend anticoagulant thromboprophylaxis with LMWH, LDUH bid, LDUH tid, or fondaparinux (Grade 1B).

2.4. For acutely ill hospitalized medical patients at low risk of thrombosis (Table 2), we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B).

2.7.1. For acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding (Table 3), we recommend against anticoagulant thromboprophylaxis (Grade 1B).

2.7.2. For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, we suggest the optimal use of mechanical thromboprophylaxis with GCS (Grade 2C) **or IPC** (Grade 2C), **rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis** (Grade 2B).

Thrombosis Risk	Bleeding risk	Recommendation	Grade
Low	Low	No prophylaxis (pharmacological or mechanical)	1B
High	Low	LMWH, LDUH (bid OR tid), Fondaparinux	1B
Any	High	Mechanical prophylaxis	2B 2C

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Western

Padua prediction model

Table 2—*Risk Factors for VTE in Hospitalized Medical Patients*[9]

Risk Factor	Points
Active cancer[a]	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility[b]	3
Already known thrombophilic condition[c]	3
Recent (≤ 1 mo) trauma and/or surgery	2
Elderly age (≥ 70 y)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥ 30)	1
Ongoing hormonal treatment	1

In the Padua Prediction Score risk assessment model, high risk of

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Western

Table 2—*Risk Factors for VTE in Hospitalized Medical Patients*[9]

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Obesity (BMI ≥ 30)	1
Ongoing hormonal treatment	1

In the Padua Prediction Score risk assessment model, high risk of

Padua prediction model

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Table 7—*Caprini Risk Assessment Model*

1 Point	2 Points	3 Points	5 Points
Age 41-60 y	Age 61-74 y	Age ≥ 75 y	Stroke (< 1 mo)
Minor surgery	Arthroscopic surgery	History of VTE	Elective arthroplasty
BMI > 25 kg/m²	Major open surgery (> 45 min)	Family history of VTE	Hip, pelvis, or leg fracture
Swollen legs	Laparoscopic surgery (> 45 min)	Factor V Leiden	Acute spinal cord injury (< 1 mo)
Varicose veins	Malignancy	Prothrombin 20210A	
Pregnancy or postpartum	Confined to bed (> 72 h)	Lupus anticoagulant	
History of unexplained or recurrent spontaneous abortion	Immobilizing plaster cast	Anticardiolipin antibodies	
Oral contraceptives or hormone replacement	Central venous access	Elevated serum homocysteine	
Sepsis (< 1 mo)		Heparin-induced thrombocytopenia	
Serious lung disease, including pneumonia (< 1 mo)		Other congenital or acquired thrombophilia	
Abnormal pulmonary function			
Acute myocardial infarction			
Congestive heart failure (< 1 mo)			
History of inflammatory bowel disease			
Medical patient at bed rest			

Very low (0-1 point), low (2 points), moderate (3-4 points), or high (5 points)

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Table 7—*Caprini Risk Assessm*

1 Point	2 Points	
Age 41-60 y	Age 61-74 y	Age ≥ 7
Minor surgery	Arthroscopic surgery	History
BMI > 25 kg/m²	Major open surgery (> 45 min)	Family
Swollen legs	Laparoscopic surgery (> 45 min)	Factor
Varicose veins	Malignancy	Prothro
Pregnancy or postpartum	Confined to bed (> 72 h)	Lupus
History of unexplained or recurrent spontaneous abortion	Immobilizing plaster cast	Anticar
Oral contraceptives or hormone replacement	Central venous access	Elevate
Sepsis (< 1 mo)		Heparin
Serious lung disease, including pneumonia (< 1 mo)		Other c throt
Abnormal pulmonary function		
Acute myocardial infarction		
Congestive heart failure (< 1 mo)		
History of inflammatory bowel disease		
Medical patient at bed rest		

5 Points
Stroke (< 1 mo)
Elective arthroplasty
Hip, pelvis, or leg fracture
Acute spinal cord injury (< 1 mo)

Very low (0-1 point), low (2 points), moderate (3-4 points), or high (5 points)

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Caprini Score in Practice

- Validated at U Michigan in 8216 surgery pts
- VTE risk increased with score, p<0.01
- But most patients qualify for drugs
- Compliance poor

Risk Level	%	VTE Risk %	Rec Proph.	Actual Proph. %	Compliance %
Highest	52.1	1.94	Drug+IPC	32	27
High	36.5	0.97	Drug	25	25
Moderate	10.4	0.70	Drug or IPC	15	79
Low	0.9	0.00	Ambulate	8	100

Bahl, Ann Surg 2010

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Are the risk factors the same?

- Risk stratification
  - Similar risk factors in Asian and Western patients

Blood Coagulation, Fibrinolysis and Cellular Haemostasis © Schattauer 2011

Risk factors for symptomatic venous thromboembolism in Thai hospitalised medical patients

Ponlapat Rojnuckarin[1]; Noppacharn Uaprasert[1]; Laddawan Vajragupta[2]; Numphung Numkarunarunrote[2]; Nathaporn Tanpowpong[2]; Pranee Sutcharitchan[1]

[1]Department of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [2]Radiology, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Thrombosis and Haemostasis 106.6/2011

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Blood Coagulation, Fibrinolysis and Cellular Haemostasis © Schattauer 2011

Risk factors for symptomatic venous thromboembolism in Thai hospitalised medical patients

Table 2: A multivariate analysis for the risk factors for venous thromboembolism (VTE) in medical patients (N=1,290).

Risk factors	Relative risk (95% CI)	P-value
Autoimmune disease	11.83 (3.89–35.97)	<0.001
Solid tumours	4.66 (1.84–11.79)	0.001
Family history of VTE	120.28 (6.89–2101)	0.001
Varicose vein	40.09 (3.75–429.27)	0.002
Oestrogen	17.08 (1.18–248.20)	0.038
95% CI, 95% confidence interval.		

Thrombosis and Haemostasis 106.6/2011

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Original Article *J Atheroscler Thromb 2014*

Western

Validation of a Venous Thromboembolism Risk Assessment Model in Hospitalized Chinese Patients: A Case-Control Study

Haixia Zhou[1], Lan Wang[1], Xiaoling Wu[1], Yongjiang Tang[1], Jing Yang[1], Bo Wang[1], Yu Yan[2], Binmiao Liang[1], Ke Wang[1], Xuemei Ou[1], Maoyun Wang[1], Yulin Feng[1] and Qun Yi[1]

Table 2. Associations between the Caprini risk levels and risk of VTE

Risk level	Cases (n=347), n (%)	Controls (n=651), n (%)	p value	OR for VTE (95% CI)	Adjusted OR for VTE (95% CI) ‡
Low risk (0-1)	31 (8.9)	120 (18.4)	< 0.0001 *	1.00 (Reference)	1.00 (Reference)
Moderate risk (2)	44 (12.7)	125 (19.2)		1.36 (0.81-2.30)	1.43 (0.84-2.41)
High risk (3-4)	105 (30.3)	263 (40.4)		1.55 (0.98-2.44)	1.65 (1.05-2.61)
Highest risk (≥ 5)	167 (48.1)	143 (22.0)		4.55 (2.89-7.17)	4.84 (3.06-7.64)
Highest risk with Score 5-6	95 (27.4)	117 (18.0)	–	3.14 (1.95-5.07)	3.33 (2.06-5.40)
Highest risk with Score 7-8	47 (13.5)	22 (3.4)	–	8.27 (4.35-15.72)	9.41 (4.90-18.08)
Highest risk with score ≥ 9	25 (7.2)	4 (0.6)	–	24.19 (7.84-74.67)	24.69 (7.98-76.40)
Average Caprini cumulative risk score, mean ± SD	4.69 ± 2.58	3.16 ± 1.82	< 0.0001 †	–	–

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Original Article *J Atheroscler Thromb 2014*

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High risk (3-4)	105 (30.3)	263 (40.4)		1.55 (0.98-2.44)	1.65 (1.05-2.61)
Highest risk (≥ 5)	167 (48.1)	143 (22.0)		4.55 (2.89-7.17)	4.84 (3.06-7.64)
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Online version at http://www.minervamedica.it

International Angiology 2017 February;36(1):1-20
DOI: 10.23736/S0392-9590.16.03765-2

GUIDELINES

Asian venous thromboembolism guidelines: updated recommendations for the prevention of venous thromboembolism

Ngoh C. LIEW[1]*, Gina V. ALEMANY[2], Pantep ANGCHAISUKSIRI[3], Soo-Mee BANG[4], Gordon CHOI[5], Deidre A. DE SILVA[6], Ji M. HONG[7], Limi LEE[1], Yong J. LI[8], Ganesan N. RAJAMONEY[9], John SUVIRAJ[10], Thiam C. TAN[11], Eric TSE[12], Li T. TEO[13], Julie VISPERAS[14], Raymond S. WONG[15], Lai H. LEE[16]

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Western

Asian venous thromboembolism guidelines: updated recommendations for the prevention of venous thromboembolism

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TABLE II.—*Risk stratification.*[31]

Risk category	Frequency of calf vein thrombosis (%)	Frequency of proximal vein thrombosis (%)	Frequency of fatal PE (%)
High	40-80	10-30	>1
Moderate	10-40	1-10	0.1-1
Low	<10	<1	<0.1

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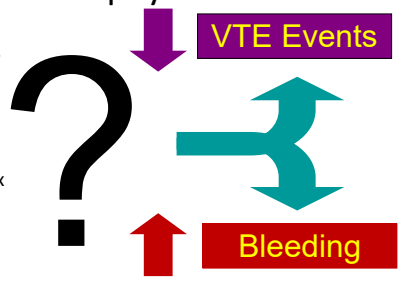
Western

Prophylaxis

- Mechanical
  - GCS, IPC, VFP
- Pharmacological
  - UFH
  - LMWH
  - Fondaparinux
  - Warfarin
  - DOACs ????



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Western

Table 3—*Independent Risk Factors for Bleeding in 10,866 Hospitalized Medical Patient*[10]

Risk Factor[a]	Total Patients, No. (%) (N = 10,866)	OR (95% CI)
Active gastroduodenal ulcer	236 (2.2)	4.15 (2.21-7.77)
Bleeding in 3 mo before admission	231 (2.2)	3.64 (2.21-5.99)
Platelet count < 50 × 10⁹/L	179 (1.7)	3.37 (1.84-6.18)
Age ≥ 85 y (vs < 40 y)	1,178 (10.8)	2.96 (1.43-6.15)
Hepatic failure (INR > 1.5)	219 (2.0)	2.18 (1.10-4.33)
Severe renal failure (GFR < 30 mL/min/m²)	1,084 (11.0)	2.14 (1.44-3.20)
ICU or CCU admission	923 (8.5)	2.10 (1.42-3.10)
Central venous catheter	820 (7.5)	1.85 (1.18-2.90)
Rheumatic disease	740 (6.8)	1.78 (1.09-2.89)
Current cancer	1,166 (10.7)	1.78 (1.20-2.63)
Male sex	5,367 (49.4)	1.48 (1.10-1.99)

Data shown were obtained by multiple logistic regression analysis for characteristics at admission independently associated with in-hospital bleeding (major bleeding and clinically relevant nonmajor bleeding combined). GFR = glomerular filtration rate; INR = international normalized ratio.
[a]Although not specifically studied in medical patients, one would also expect dual antiplatelet therapy to increase the risk of bleeding.

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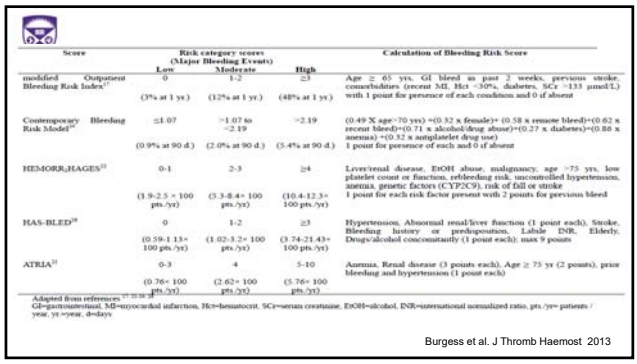

Score	Risk category scores (Major Bleeding Events) Low	Moderate	High	Calculation of Bleeding Risk Score
modified Outpatient Bleeding Risk Index[17]	0 (3% at 1 yr.)	1-2 (12% at 1 yr.)	≥3 (48% at 1 yr.)	Age ≥ 65 yrs, GI bleed in past 2 weeks, previous stroke, comorbidities (recent MI, Hct <30%, diabetes, SCr >133 μmol/L) with 1 point for presence of each condition and 0 if absent
Contemporary Bleeding Risk Model[18]	≤1.07 (0.9% at 90 d.)	>1.07 to <2.19 (2.0% at 90 d.)	>2.19 (3.4% at 90 d.)	(0.49 X age−70 yrs) +(0.32 x female)+ (0.58 x remote bleed)+(0.62 x recent bleed)+(0.71 x alcohol/drug abuse)+(0.27 x diabetes)+(0.88 x anemia) +(0.32 x antiplatelet drug use) 1 point for presence of each and 0 if absent
HEMORR$_2$HAGES[11]	0-1 (1.9-2.5 × 100 pts./yr)	2-3 (3.3-8.4× 100 pts./yr)	≥4 (10.4-12.3× 100 pts./yr)	Liver/renal disease, EtOH abuse, malignancy, age >75 yrs, low platelet count or function, rebleeding risk, uncontrolled hypertension, anemia, genetic factors (CYP2C9), risk of fall or stroke 1 point for each risk factor present with 2 points for previous bleed
HAS-BLED[19]	0 (0.59-1.13× 100 pts./yr)	1-2 (1.02-3.2× 100 pts./yr)	≥3 (3.74-21.43× 100 pts./yr)	Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly (1 point each); max 9 points
ATRIA[21]	0-3 (0.76× 100 pts./yr)	4 (2.62× 100 pts./yr)	5-10 (5.76× 100 pts./yr)	Anemia, Renal disease (3 points each), Age ≥ 75 yr (2 points), prior bleeding and hypertension (1 point each)

Adapted from references [17,18,11,19,21]
GI=gastrointestinal, MI=myocardial infarction, Hct=hematocrit, SCr=serum creatinine, EtOH=alcohol, INR=international normalized ratio, pts./yr= patients / year, yr =year, d=days

Burgess et al. J Thromb Haemost 2013

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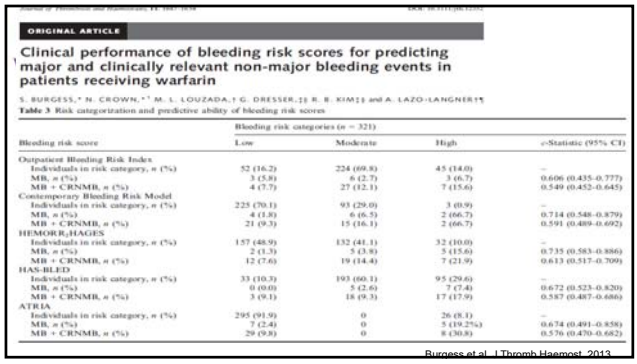

ORIGINAL ARTICLE

Clinical performance of bleeding risk scores for predicting major and clinically relevant non-major bleeding events in patients receiving warfarin

S. BURGESS,* N. CROWN,*† M. L. LOUZADA,† G. DRESSER,‡§ R. B. KIM‡§ and A. LAZO-LANGNER¶

Table 3 Risk categorization and predictive ability of bleeding risk scores

Bleeding risk score	Bleeding risk categories (n = 321) Low	Moderate	High	c-Statistic (95% CI)
Outpatient Bleeding Risk Index				
Individuals in risk category, n (%)	52 (16.2)	224 (69.8)	45 (14.0)	–
MB, n (%)	3 (5.8)	6 (2.7)	3 (6.7)	0.606 (0.435–0.777)
MB + CRNMB, n (%)	4 (7.7)	27 (12.1)	7 (15.6)	0.549 (0.452–0.645)
Contemporary Bleeding Risk Model				
Individuals in risk category, n (%)	225 (70.1)	93 (29.0)	3 (0.9)	–
MB, n (%)	4 (1.8)	6 (6.5)	2 (66.7)	0.714 (0.548–0.879)
MB + CRNMB, n (%)	21 (9.3)	15 (16.1)	2 (66.7)	0.591 (0.489–0.692)
HEMORR$_2$HAGES				
Individuals in risk category, n (%)	157 (48.9)	132 (41.1)	32 (10.0)	–
MB, n (%)	2 (1.3)	5 (3.8)	5 (15.6)	0.735 (0.583–0.886)
MB + CRNMB, n (%)	12 (7.6)	19 (14.4)	7 (21.9)	0.613 (0.517–0.709)
HAS-BLED				
Individuals in risk category, n (%)	33 (10.3)	193 (60.1)	95 (29.6)	–
MB, n (%)	0 (0.0)	5 (2.6)	7 (7.4)	0.672 (0.523–0.820)
MB + CRNMB, n (%)	3 (9.1)	18 (9.3)	17 (17.9)	0.587 (0.487–0.686)
ATRIA				
Individuals in risk category, n (%)	295 (91.9)	0	26 (8.1)	–
MB, n (%)	7 (2.4)	0	5 (19.2%)	0.674 (0.491–0.858)
MB + CRNMB, n (%)	29 (9.8)	0	8 (30.8)	0.576 (0.470–0.682)

Burgess et al. J Thromb Haemost 2013

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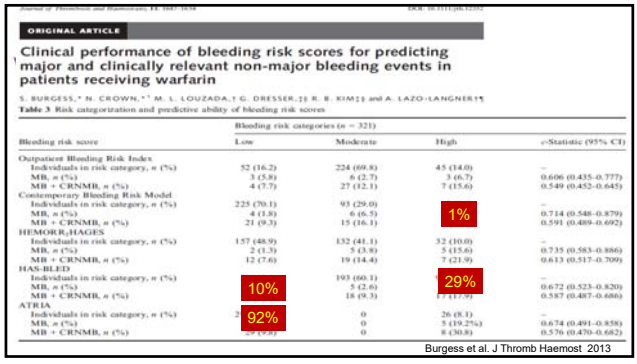

ORIGINAL ARTICLE

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ATRIA				
Individuals in risk category, n (%)	92%	0	26 (8.1)	–
MB, n (%)		0	5 (19.2%)	0.674 (0.491–0.858)
MB + CRNMB, n (%)		0	8 (30.8)	0.576 (0.470–0.682)

1%

Burgess et al. J Thromb Haemost 2013

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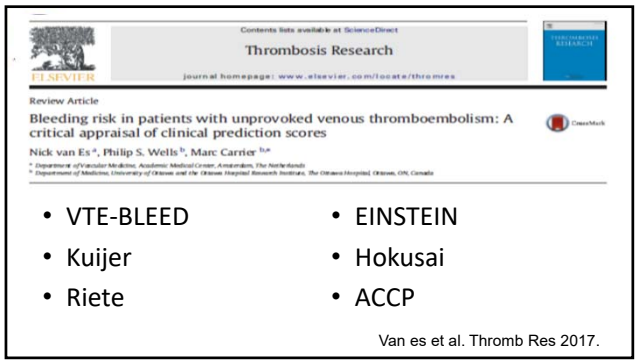

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Bleeding risk in patients with unprovoked venous thromboembolism: A critical appraisal of clinical prediction scores

Nick van Es [a], Philip S. Wells [b], Marc Carrier [b,*]

- VTE-BLEED
- Kuijer
- Riete
- EINSTEIN
- Hokusai
- ACCP

Van es et al. Thromb Res 2017.

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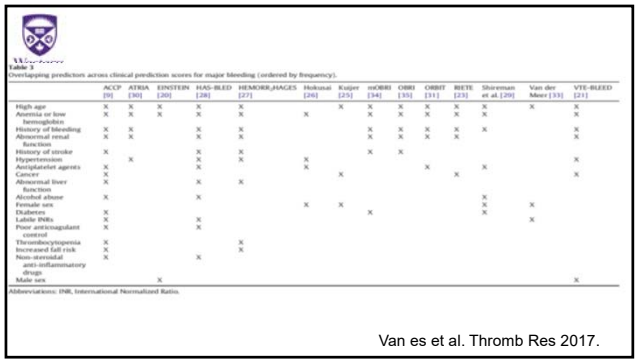

Table 3
Overlapping predictors across clinical prediction scores for major bleeding (ordered by frequency).

	ACCP [9]	ATRIA [30]	EINSTEIN [20]	HAS-BLED [28]	HEMORR2HAGES [27]	Hokusai [26]	Kuijer [25]	mOBRI [34]	OBRI [35]	ORBIT [31]	RIETE [23]	Shireman et al. [29]	Van der Meer [33]	VTE-BLEED [21]
High age	X	X	X	X	X		X	X	X	X	X	X	X	X
Anemia or low hemoglobin	X	X	X	X	X	X		X	X	X	X	X		X
History of bleeding	X	X		X	X			X	X	X	X	X		X
Abnormal renal function	X	X		X	X			X	X	X	X			X
History of stroke	X			X	X			X	X					
Hypertension		X		X	X	X								X
Antiplatelet agents	X			X		X				X		X		
Cancer	X						X				X			X
Abnormal liver function	X			X	X									
Alcohol abuse	X			X								X		
Female sex						X	X					X	X	
Diabetes	X							X				X		
Labile INRs	X			X									X	
Poor anticoagulant control	X			X										
Thrombocytopenia	X				X									
Increased fall risk	X				X									
Non-steroidal anti-inflammatory drugs	X			X										
Male sex			X											X

Abbreviations: INR, International Normalized Ratio.

Van es et al. Thromb Res 2017.

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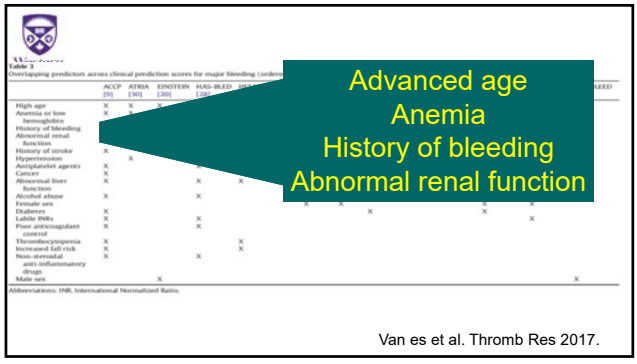

Table 3
Overlapping predictors across clinical prediction scores for major bleeding (ordered

Advanced age
Anemia
History of bleeding
Abnormal renal function

Van es et al. Thromb Res 2017.

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Agenda

- Why do clots matter?
  - Overview of VTE
- What is the incidence of VTE in stroke patients?
  - Epidemiology of VTE after stroke
- How do we prevent VTE in stroke patients?
  - Is anticoagulant prophylaxis effective?
  - Is anticoagulant prophylaxis safe?

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Asian venous thromboembolism guidelines: updated recommendations for the prevention of venous thromboembolism

Ngoh C. LIEW[1,*], Gina V. ALEMANY[2], Pantep ANGCHAISUKSIRI[3], Soo-Mee BANG[4], Gordon CHOI[5], Deidre A. DE SILVA[6], Ji M. HONG[7], Limi LEE[1], Yong J. LI[8], Ganesan N. RAJAMONEY[9], John SUVIRAJ[10], Thiam C. TAN[11], Eric TSE[12], Li T. TEO[13], Julie VISPERAS[14], Raymond S. WONG[15], Lai H. LEE[16]

- A general assessment of VTE and bleeding risk is recommended prior to initiation of VTE prophylaxis in ischemic and hemorrhagic stroke patients
- We recommend against the use of GCS in both ischemic and hemorrhagic stroke patients
- VTE prophylaxis options for ischemic stroke patients are IPC use or pharmacological regimens with SC LMWH
- IPC is recommended for hemorrhagic stroke patients.

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VTE prophylaxis in stroke

- McCarthy 1977
  - UFH
- McCarthy 1986
  - Unblinded RCT
  - 305 pts.
  - UFH 5000 tid x 14 d
  - PE reduction: 20% → 5%
  - DVT reduction: 73% → 22%
  - 3 mo. Mortality reduction: 33% → 21%
- TOAST Investigators 1998
  - Double blinded RCT
  - 1281 pts.
  - IV Danaparoid vs placebo
  - DVT: 0.3% vs 1.6%
  - PE: 0.3% vs 0.6%

Coull et al. Stroke 2002.
TOAST Investigators. JAMA 1998.

75

VTE prophylaxis in stroke

- CAST
  - 21,106 pts.
  - 4 weeks of ASA
  - Death, dependence, recurrence
  - Clinical diagnosis
- IST
  - 19,435 pts.
  - 3 x 2 factorial
  - UFH (Hi-Low-No) ASA
  - Death @ 14 d, death or dependency @ 6 mo

	Aspirin N (%)	Placebo N (%)
Total PE	12 (0.1)	20 (0.2)
Fatal PE	5 (0.1)	10 (0.1)

	Heparin N (%)	No Heparin N (%)
Total PE	Not significant	
Fatal PE	36 (0.4)	39 (0.4)

CAST Collaborative Group. Lancet 1997.
International Stroke Trial Collaborative Group. Lancet 1997

76

VTE prophylaxis in stroke

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	Aspirin N (%)	Placebo N (%)
Total PE	12 (0.1)	(0.2)
Fatal PE	5 (0.1)	10 (0.1)

P=0.02

	Heparin N (%)	No Heparin N (%)
Total PE	53 (0.5)	81 (0.8)
Fatal PE	36 (0.4)	39 (0.4)

CAST Collaborative Group. Lancet 1997.
International Stroke Trial Collaborative Group. Lancet 1997

77

The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison

David G Sherman, Gregory W Albers, Christopher Bladin, Cesare Fieschi, Alberto A Gabbai, Carlos S Kase, William O'Riordan, Graham F Pineo, on behalf of the PREVAIL Investigators*

Lancet 2007; 369: 1347-55

- Randomized controlled trial
- 1762 patients
  - Enoxaparin 40 mg daily
  - UFH 5000 SC BID

78

Efficacy

	Enoxaparin (n=666)	Unfractionated heparin (n=669)	Relative risk (95% CI)*	p†	Difference (95% CI)
VTE	68 (10%)	121 (18%)	0·57 (0·44–0·76)	0·0001	-7·9% (-11·6 to -4·2)
PE‡	1 (<1%)	6 (1%)	0·17 (0·02–1·39)	0·059	-0·7% (-1·5 to 0)
Symptomatic VTE	2 (<1%)	7 (1%)	0·29 (0·06–1·38)	0·096	-0·7% (-1·6 to 0·1)
Symptomatic DVT	1 (<1%)	4 (1%)	0·25 (0·03–2·24)	0·18	-0·4% (-1·1 to 0·2)
Asymptomatic DVT§	66 (10%)	114 (17%)	0·57 (0·43–0·75)	<0·0001	-7·1% (-10·8 to -3·5)
All DVT	67 (10%)	118 (18%)	0·57 (0·43–0·75)	<0·0001	-7·6% (-11·3 to -3·9)
Proximal	30 (5%)	64 (10%)	0·47 (0·31–0·72)	0·0003	-5·1% (-7·8 to -2·3)
Distal	44 (7%)	85 (13%)	0·52 (0·37–0·74)	0·0002	-6·1% (-9·2 to -2·9)
Proximal and distal¶	7 (1%)	31 (5%)	0·23 (0·10–0·51)	<0·0001	-3·6% (-5·4 to -1·8)

79

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Cochrane Library

Cochrane Database of Systematic Reviews

Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke (Review)

Sandercock PAG, Leong TS

- 9 trials → 3137 participants
- UFH or heparinoids (danaparoid)

Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD000119.

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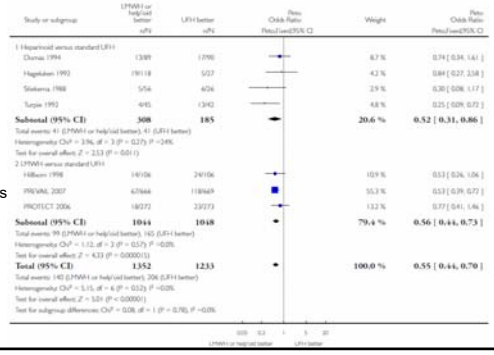
Deep Vein Thrombosis



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- Why do clots matter?
  - Overview of VTE
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  - Epidemiology of VTE after stroke
- How do we prevent VTE in stroke patients?
  - Is anticoagulant prophylaxis effective?
  - Is anticoagulant prophylaxis safe?

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Hemorrhage in stroke

- UFH
  - IST

25% of patients UFH
12,500 U SC CID

  - Hemorrhagic stroke: 1.2% vs. 0.4% (UFH vs. no UFH)
  - Fatal or transfusion: 1.3% vs. 0.4% (UFH vs. no UFH)
  - Medium vs low dose UFH
    - Hemorrhagic strokes 1.8 vs 0.7%
  - Low dose vs no UFH
    - Transfused or fatal extracranial 0.6 vs 0.4%

International Stroke Trial Collaborative Group. Lancet 1997.
Coull et al. Stroke 2002.

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The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison

	Enoxaparin (n=877)	Unfractionated heparin (n=872)	Relative risk (95% CI)	p*	Difference (95% CI)
Bleeding at end of treatment + 48 h					
Total†	69 (8%)	70 (8%)	0·98 (0·71–1·35)	0·90	−0·2% (−2·7% to 2·4)
Symptomatic intracranial haemorrhage	4 (1%)	6 (1%)	0·66 (0·19–2·34)	0·55	−0·2% (−0·9% to 0·5)
Death of patient with symptomatic intracranial haemorrhage	3 (<1%)	4 (1%)	..	..	−0·1% (−0·7% to 0·5)
Major extracranial haemorrhage‡	7 (1%)	0	..	0·015	0·8% (0·2% to 1·4)
Resulting in death	2 (<1%)	0	..	..	0·2% (−0·1% to 0·5)
Drop of haemoglobin ≥30 g/L	7 (1%)	0	..	..	0·8% (0·2% to 1·4)
Transfusion of ≥2 units of blood	5 (1%)	0	..	..	0·6% (0·1% to 1·1)
Clinically important haemorrhage	11 (1%)	6 (1%)	1·82 (0·68–4·91)	0·23	0·6% (−0·4% to 1·5)
Death of patient with clinically important haemorrhage§	5 (1%)	4 (1%)	1·24 (0·33–4·65)	1·0	0·1% (−0·6% to 0·8)
Minor extracranial haemorrhage¶	42 (5%)	48 (6%)	0·87 (0·58–1·30)	0·50	−0·7% (−2·8% to 1·4)
All-cause mortality up to day 14	48 (6%)	45 (5%)	1·12‖ (0·75–1·69)	0·58**	..
All-cause mortality up to day 90	100 (12%)	103 (12%)	1·01‖ (0·77–1·33)	0·96**	..

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Cochrane Library
Cochrane Database of Systematic Reviews

Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke (Review)

Sandercock PAG, Leong TS

- 9 trials → 3137 participants
- UFH or heparinoids (danaparoid)

Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD000119.

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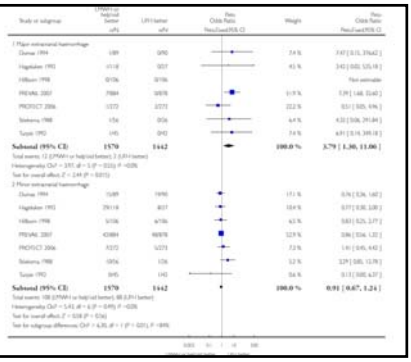
Extracranial Hemorrhage



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Hemorrhage in stroke

- Risk factors
  - Leukoaraiosis HR 2.7 (95% CI 1.4, 5.3)
  - Age > 65 y HR 1.9 (95% CI 1.0, 3.4)
  - Intensity of anticoagulation (warfarin)
  - Hypertension
  - Congophilic angiopathy

Gorter. Neurology 1999.

88

Relative contraindications to prophylaxis

- Recent CNS bleed
- Intracranial or spinal lesion at high risk for bleeding
- Active bleeding
- Chronic clinically significant bleeding
- Platelet count <50,000, platelet dysfunction
- Recent major operation at risk for bleeding
- Underlying coagulopathy
- Spinal anesthesia / LP
- High fall risk

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SO, CAN WE USE OTHER STRATEGIES?

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TED stockings DON'T work !

Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial

*The CLOTS Trials Collaboration**

www.thelancet.com Vol 373 June 6, 2009

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Clots in Legs Or sTockings after Stroke

- RCT
  - Stroke admission
  - Thigh-length GCS (Covidien) vs avoid GCS
  - All received routine care
- Primary outcome
  - Definite or probable symptomatic or asymptomatic DVT - proximal

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	Thigh-length GCS (n=1256)	Avoid GCS (n=1262)	Odds ratio (95% CI)
Primary outcome			
Proximal DVT	126 (10·0%)	133 (10·5%)	..
Alive and free of primary outcome	974 (77·5%)	1000 (79·2%)	..
Dead before any primary outcome	115 (9·2%)	101 (8·0%)	..
Missing	41 (3·3%)	28 (2·2%)	..
Unadjusted (dead and missing excluded)	..	..	0·97 (0·75–1·26)
Adjusted* (dead and missing excluded)	..	..	0·98 (0·76–1·27)
Secondary outcomes by 30 days or later second compression Doppler ultrasound			
Dead by 30 days	122 (9·7%)	110 (8·7%)	1·13 (0·86–1·48)
Symptomatic proximal DVT	36 (2·9%)	43 (3·4%)	0·84 (0·53–1·31)
Asymptomatic proximal DVT	90 (7·2%)	90 (7·1%)	1·01 (0·74–1·36)
Symptomatic DVT (proximal or distal)	55 (4·4%)	61 (4·8%)	0·90 (0·62–1·31)
Any DVT (proximal or distal)	205 (16·3%)	224 (17·7%)	0·90 (0·73–1·11)
PE confirmed on imaging or autopsy	13 (1·0%)	20 (1·6%)	0·65 (0·32–1·31)
PE on autopsy	1 (0·1%)	1 (0·1%)	1·00 (0·06–16·08)
Any DVT or PE	213 (17·0%)	232 (18·4%)	0·91 (0·74–1·11)
Skin breaks/ulcers/blisters/skin necrosis	64 (5·1%)	16 (1·3%)	4·18 (2·40–7·27)
Lower limb ischaemia/amputation	7 (0·6%)	2 (0·2%)	3·53 (0·73–17·03)
Primary outcomes within 14 days			
Post-hoc analysis restricting follow-up to 14 days†	87 (6·9%)	95 (7·5%)	..
Unadjusted (dead and missing excluded)	..	..	0·95 (0·70–1·28)
Adjusted* (dead and missing excluded)	..	..	0·95 (0·70–1·29)

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Western

Annals of Internal Medicine | ORIGINAL RESEARCH

Thigh-Length Versus Below-Knee Stockings for Deep Venous Thrombosis Prophylaxis After Stroke

A Randomized Trial

The CLOTS (Clots in Legs Or sTockings after Stroke) Trial Collaboration*

2 November 2010 | Annals of Internal Medicine | Volume 153 • Number 9

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Table 2. **Primary and Secondary Outcomes**

Outcome	Thigh-Length Stockings Group (n = 1552), n (%)	Below-Knee Stockings Group (n = 1542), n (%)	Difference in Proportion (95% CI), percentage points	Adjusted Odds Ratio (95% CI)*	P Value From Logistic Regression
Primary outcome					
Proximal DVT	98 (6.3)	138 (8.8)	−2.5 (−0.7 to −4.4)	0.69 (0.53 to 0.91)	0.008
Alive and free of primary outcome	1246 (80.3)	1213 (77.7)			
Died before any primary outcome	170 (10.9)	161 (10.3)			
Missing†	38 (2.4)	50 (3.2)			

Table 4. **Adverse Events**

Outcome	Thigh-Length Stockings Group (n = 1552)	Below-Knee Stockings Group (n = 1542)	Difference in Proportion (95% CI), percentage points	Odds Ratio (95% CI)	P Value From Odds Ratio
Died by day 30, n (%)	182 (11.7)	174 (11.1)	0.6 (−1.6 to 2.8)	1.05 (0.84 to 1.31)	0.67
Patients with discharge form, n (%)	1550 (99.9)	1560 (99.9)			
Median length of hospital stay (IQR), d	10 (10 to 12)	10 (10 to 12)			0.465
Adverse events, n (%)†					
Low-severity skin problems	75 (4.8)	56 (3.6)	1.2 (−0.2 to 2.7)	1.37 (0.96 to 1.94)	0.08
Patients with skin breaks, ulcers, blisters, or necrosis	61 (3.9)	45 (2.9)	1.0 (−0.2 to 2.3)	1.38 (0.93 to 2.04)	0.11
Lower-limb ischemia or amputation	4 (0.3)	7 (0.4)	−0.2 (−0.6 to 0.2)	0.57 (0.17 to 2.0)	0.38
Any skin problem	140 (9.0)	108 (6.9)	2.0 (0.1 to 3.9)	1.33 (1.03 to 1.73)	0.03

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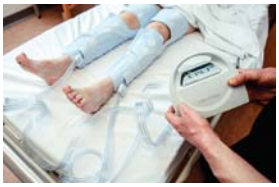
Western

Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial

Lancet 2013; 382: 516–24

CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration*

- RCT
  - IPC vs No IPC
- 2876 patients with
  - Stroke within 3 days
  - Immobile



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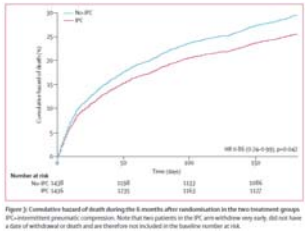
CLOTS 3

Primary Outcome

- Proximal DVT
  - IPC 8.5%
  - No IPC 12.1%
  - Absolute risk reduction 3.6%
  - Use of LMWH or UFH 30%



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Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis

Y.M. Arabi, F. Al-Hameed, K.E.A. Burns, S. Mehta, S.J. Alsolamy, M.S. Alshahrani, Y. Mandourah, G.A. Almekhlafi, M. Almaani, A. Al Bshabshe, S. Finfer, Z. Arshad, I. Khalid, Y. Mehta, A. Gaur, H. Hawa, H. Buscher, H. Lababidi, A. Al Aithan, S.A.I. Abdukahil, J. Jose, L.Y. Afesh, and A. Al-Dawood, for the Saudi Critical Care Trials Group*

N ENGL J MED 380;14 NEJM.ORG APRIL 4, 2019

PREVENT Study

- RCT
  - Patients admitted to ICU
  - Pharmacological prophylaxis +/- IPC
  - Outcome: DVT @ day 28
  - 2014 – 2018
  - 2003 patients randomized

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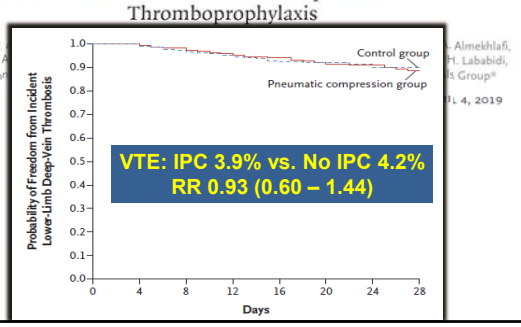
Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis



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Role of IVC filters

- Levin 1993
  - 42 IVCF pts. → 62% complications
  - 12% PE
  - 57%
    - IVC or filter thrombosis
    - Recurrent DVT
    - Post-phlebitic syndrome

Levin et al. Neurology 1993.

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Role of IVC filters

- Schiff & DeAngelis 1994
  - 51 pts. w/ Brain metastasis and VTE
  - 10 IVC filters → 4 VTE recurrence
- Olin 1987
  - 49 pts. w / Brain neoplasia and VTE
  - 24 IVCF
    - 1 developed PE
  - 25 anticoagulants
    - 2 bleeding (1 ICH)
  - No difference in survival

Schiff & DeAngelis. Cancer 1994.
Olin et al. Arch Intern Med 1987.

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JAMA Network | Open.

Original Investigation | Cardiology

Association of Inferior Vena Cava Filter Placement for Venous Thromboembolic Disease and a Contraindication to Anticoagulation With 30-Day Mortality

Tyson E. Turner, MD, MPH; Mohammed J. Saeed, MBChB, MPH; Eric Novak, MS; David L. Brown, MD

- 126,030 VTE patients (USA: CA, FL, NY)
  - 45,771 IVC filter

IVC filter → HR for 30-day mortality 1.18 (1.13-1.22)

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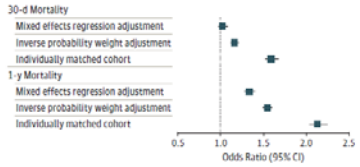
LESS IS MORE

Association of Inferior Vena Cava Filter Use With Mortality Rates in Older Adults With Acute Pulmonary Embolism

Behnood Bikdeli, MD
Yun Wang, PhD
David Jimenez, MD, PhD
Joseph S. Ross, MD, MHS
Manuel Monreal, MD, PhD
Samuel Z. Goldhaber, MD
Harlan M. Krumholz, MD, SM

Figure. Association Between Use of Inferior Vena Cava Filters and 30-Day and 1-Year Mortality Across 3 Different Statistical Adjustment Methods



JAMA Internal Medicine February 2019 Volume 179, Number 2

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What about DOACs?

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What about DOACs?

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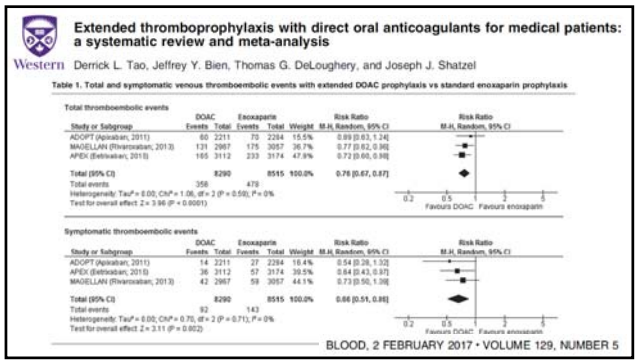

Extended thromboprophylaxis with direct oral anticoagulants for medical patients: a systematic review and meta-analysis

Western

Derrick L. Tao, Jeffrey Y. Bien, Thomas G. DeLoughery, and Joseph J. Shatzel

Table 1. Total and symptomatic venous thromboembolic events with extended DOAC prophylaxis vs standard enoxaparin prophylaxis

Total thromboembolic events

Study or Subgroup	DOAC Events	DOAC Total	Enoxaparin Events	Enoxaparin Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT (Apixaban, 2011)	60	2211	70	2284	15.5%	0.89 [0.63, 1.24]
MAGELLAN (Rivaroxaban; 2013)	131	2967	175	3057	36.7%	0.77 [0.62, 0.96]
APEX (Betrixaban; 2015)	165	3112	233	3174	47.9%	0.72 [0.60, 0.86]
Total (95% CI)		8290		8515	100.0%	0.76 [0.67, 0.87]
Total events	358		478			

Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 3.96 (P < 0.0001)

Risk Ratio M-H, Random, 95% CI: 0.2, 0.5, 1, 2, 5 — Favours DOAC, Favours enoxaparin

Symptomatic thromboembolic events

Study or Subgroup	DOAC Events	DOAC Total	Enoxaparin Events	Enoxaparin Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT (Apixaban, 2011)	14	2211	27	2284	18.4%	0.54 [0.28, 1.02]
APEX (Betrixaban; 2015)	36	3112	57	3174	39.5%	0.64 [0.43, 0.97]
MAGELLAN (Rivaroxaban; 2013)	42	2967	59	3057	44.1%	0.73 [0.50, 1.06]
Total (95% CI)		8290		8515	100.0%	0.66 [0.51, 0.86]
Total events	92		143			

Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 3.11 (P = 0.002)

Risk Ratio M-H, Random, 95% CI: 0.2, 0.5, 1, 2, 5 — Favours DOAC, Favours enoxaparin

BLOOD, 2 FEBRUARY 2017 • VOLUME 129, NUMBER 5

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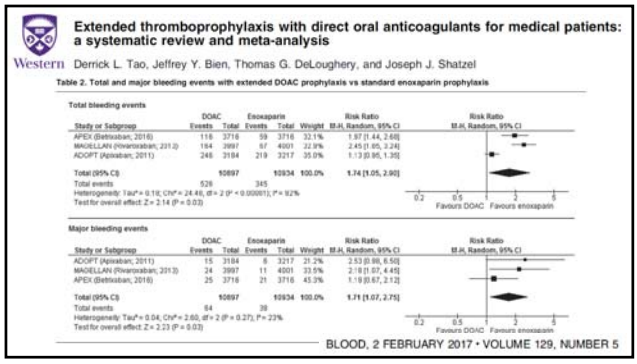

Extended thromboprophylaxis with direct oral anticoagulants for medical patients: a systematic review and meta-analysis

Western

Derrick L. Tao, Jeffrey Y. Bien, Thomas G. DeLoughery, and Joseph J. Shatzel

Table 2. Total and major bleeding events with extended DOAC prophylaxis vs standard enoxaparin prophylaxis

Total bleeding events

Study or Subgroup	DOAC Events	DOAC Total	Enoxaparin Events	Enoxaparin Total	Weight	Risk Ratio M-H, Random, 95% CI
APEX (Betrixaban; 2016)	118	3716	59	3716	32.1%	1.97 [1.44, 2.68]
MAGELLAN (Rivaroxaban; 2013)	194	3997	97	4001	22.9%	2.45 [1.95, 3.24]
ADOPT (Apixaban; 2011)	246	3184	219	3217	35.0%	1.13 [0.95, 1.35]
Total (95% CI)		10897		10934	100.0%	1.74 [1.05, 2.90]
Total events	526		345			

Heterogeneity: Tau² = 0.18; Chi² = 24.48, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.14 (P = 0.03)

Risk Ratio M-H, Random, 95% CI: 0.2, 0.5, 1, 2, 5 — Favours DOAC, Favours enoxaparin

Major bleeding events

Study or Subgroup	DOAC Events	DOAC Total	Enoxaparin Events	Enoxaparin Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT (Apixaban; 2011)	15	3184	8	3217	21.2%	2.53 [0.99, 6.50]
MAGELLAN (Rivaroxaban; 2013)	24	3997	11	4001	33.5%	2.18 [1.07, 4.45]
APEX (Betrixaban; 2016)	25	3716	21	3716	45.3%	1.19 [0.67, 2.12]
Total (95% CI)		10897		10934	100.0%	1.71 [1.07, 2.75]
Total events	64		38			

Heterogeneity: Tau² = 0.04; Chi² = 2.60, df = 2 (P = 0.27); I² = 23%
Test for overall effect: Z = 2.23 (P = 0.03)

Risk Ratio M-H, Random, 95% CI: 0.2, 0.5, 1, 2, 5 — Favours DOAC, Favours enoxaparin

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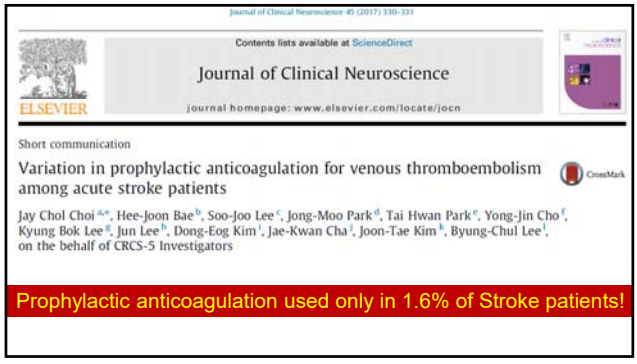

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Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Short communication

Variation in prophylactic anticoagulation for venous thromboembolism among acute stroke patients

Jay Chol Choi [a,*], Hee-Joon Bae [b], Soo-Joo Lee [c], Jong-Moo Park [d], Tai Hwan Park [e], Yong-Jin Cho [f], Kyung Bok Lee [g], Jun Lee [b], Dong-Eog Kim [i], Jae-Kwan Cha [j], Joon-Tae Kim [k], Byung-Chul Lee [l], on the behalf of CRCS-5 Investigators

Prophylactic anticoagulation used only in 1.6% of Stroke patients!

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Unresolved issues

- Barriers to implementation
- Optimal risk stratification
- Specific subgroups
  - Cancer, pregnancy, renal failure, obese, elderly
- Optimal duration
- Optimal timing

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Unresolved issues

- **Barriers to implementation**
- Optimal risk stratification
- Specific subgroups
  - Cancer, pregnancy, renal failure, obese, elderly
- Optimal duration
- Optimal timing

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Position statements

- Appropriate VTE prophylaxis is required in patients at risk
  - Agency for Healthcare Research and Quality, 2001
- Utilize clinically appropriate measures to prevent DVT/PE
  - The National Quality Forum, 2003
- The use of proven and effective DVT prevention methods could save many lives of many patients
  - JCAHO, 2004
- For every general hospital, we recommend that a formal, active strategy that addresses the prevention of VTE be developed
  - ACCP, 2008

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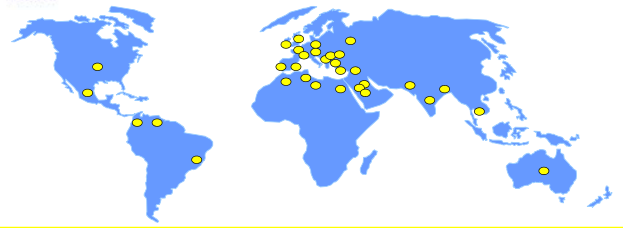
ENDORSE : WORLDWIDE

(Lancet 2008; 371: 387-394)



68,183 patients; 32 countries; 358 sites

First patient enrolled August 2, 2006;Last patient enrolled January 4, 2007

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Worldwide Prophylaxis Status for 68,183 Patients

52% at Risk for VTE
(50% receive ACCP recommended prophy)

Surgical	Medical
64% at Risk for VTE	42% at Risk for VTE
59% receive ACCP Rec. Px	40% receive ACCP Rec. Px

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E-Alerts Can Increase Prophylaxis

- 2506 hospitalized patients
- VTE risk score ≥ 4
- Randomized to intervention or control

Intervention	Treatment Received	
	Mechanical, %	Pharmacologic, %
E-Alert	10	23.6
Control	1.5	13
P-value	0.001	0.001

Kucher N, et al. *N Engl J Med*. 2005;352:969-977.

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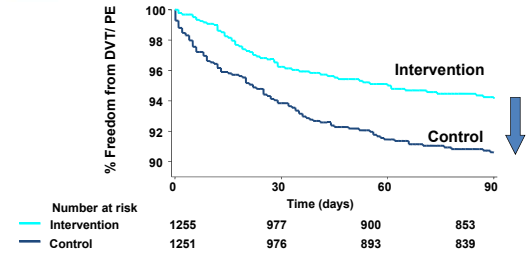
E-Alerts Decrease VTE



Kucher N, et al. *N Engl J Med* 2005;352:969-977.

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Human Alerts Increase Prophylaxis

- 2493 hospitalized patients
- VTE risk score ≥ 4
- Randomized to intervention or control

Intervention	Treatment Received	
	Mechanical, %	Pharmacologic, %
Hu-Alert	21	28
Control	8	14
95% CI	10.6-16.0	10.5-16.8

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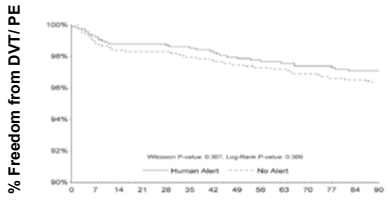
Human Alerts Decrease VTE



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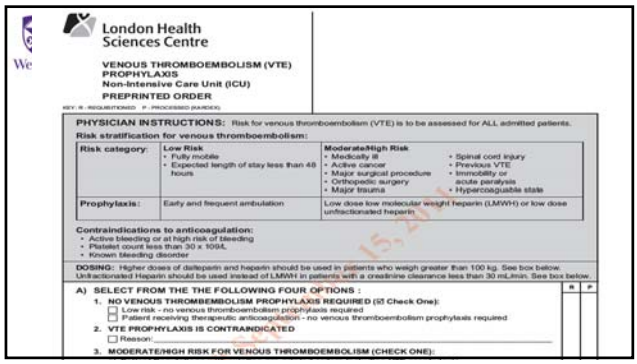

London Health Sciences Centre

VENOUS THROMBOEMBOLISM (VTE) PROPHYLAXIS
Non-Intensive Care Unit (ICU)
PREPRINTED ORDER

KEY: R - REQUISITIONED P - PROCESSED (NARDEX)

PHYSICIAN INSTRUCTIONS: Risk for venous thromboembolism (VTE) is to be assessed for ALL admitted patients.

Risk stratification for venous thromboembolism:

Risk category:	Low Risk	Moderate/High Risk
	• Fully mobile • Expected length of stay less than 48 hours	• Medically ill • Active cancer • Major surgical procedure • Orthopedic surgery • Major trauma • Spinal cord injury • Previous VTE • Immobility or acute paralysis • Hypercoagulable state
Prophylaxis:	Early and frequent ambulation	Low dose low molecular weight heparin (LMWH) or low dose unfractionated heparin

Contraindications to anticoagulation:
- Active bleeding or at high risk of bleeding
- Platelet count less than 30 x 10⁹/L
- Known bleeding disorder

DOSING: Higher doses of dalteparin and heparin should be used in patients who weigh greater than 100 kg. See box below.
Unfractionated Heparin should be used instead of LMWH in patients with a creatinine clearance less than 30 mL/min. See box below.

A) SELECT FROM THE THE FOLLOWING FOUR OPTIONS :	R	P
1. NO VENOUS THROMBEMBOLISM PROPHYLAXIS REQUIRED (☑ Check One): ☐ Low risk - no venous thromboembolism prophylaxis required ☐ Patient receiving therapeutic anticoagulation - no venous thromboembolism prophylaxis required		
2. VTE PROPHYLAXIS IS CONTRAINDICATED ☐ Reason:_____		
3. MODERATE/HIGH RISK FOR VENOUS THROMBOEMBOLISM (CHECK ONE):		

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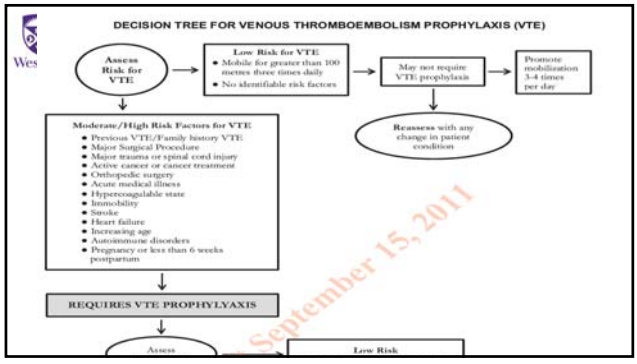
- Active bleeding or at high risk of bleeding
- Platelet count less than 30 x 10⁹/L
- Known bleeding disorder

DOSING: Higher doses of dalteparin and heparin should be used in patients who weigh greater than 100 kg. See box below.
Unfractionated Heparin should be used instead of LMWH in patients with a creatinine clearance less than 30 mL/min. See box below.

A) SELECT FROM THE THE FOLLOWING FOUR OPTIONS :	R	P
1. NO VENOUS THROMBEMBOLISM PROPHYLAXIS REQUIRED (☑ Check One): ☐ Low risk - no venous thromboembolism prophylaxis required ☐ Patient receiving therapeutic anticoagulation - no venous thromboembolism prophylaxis required		
2. VTE PROPHYLAXIS IS CONTRAINDICATED ☐ Reason:_____		
3. MODERATE/HIGH RISK FOR VENOUS THROMBOEMBOLISM (CHECK ONE): a) Patient Populations with existing pre-printed orders including VTE prophylaxis ☐ See pre-printed order set for specific patient population b) Low dose LMWH ☐ Dalteparin 5000 units subcutaneous daily ☐ Dalteparin 2500 units subcutaneous daily (for patients weighing less than 40 kg) ☐ Dalteparin 7500 units subcutaneous daily (for patients weighing more than 100 kg) c) Unfractionated Heparin (For patients with creatinine clearance less than 30 mL/min) ☐ Heparin 5000 units subcutaneous q 8 hours		
4. AT RISK FOR VENOUS THROMBOEMBOLISM BUT ALSO AT HIGH RISK FOR BLEEDING ☐ See pre-printed order set for specific patient population ☐ Intermittent pneumatic compression device (IPC) And / Or ☐ Graduated compression stockings (TEDs) ☐ MD to reassess the appropriateness of pharmacological prophylaxis ☐ tomorrow ☐ in 2 days OR ☐ Start LMHW or UFH: _____ _____ units subcutaneous on (date) _____ and discontinue IPC and/or TEDs after first dose		
B) MONITORING PLATELET COUNT: ☐ For Patients on Unfractionated Heparin Only - Platelet count Day #4 post initiation, then weekly for 2 weeks		

PRESCRIBER'S PRINTED NAME / SIGNATURE / CONTACT #		DATE (YYYY-MMM-DD)	TIME:
PROCESSOR INITIALS	DATE (YYYY-MMM-DD) TIME:	NURSE INITIALS	DATE (YYYY-MMM-DD) TIME:

119



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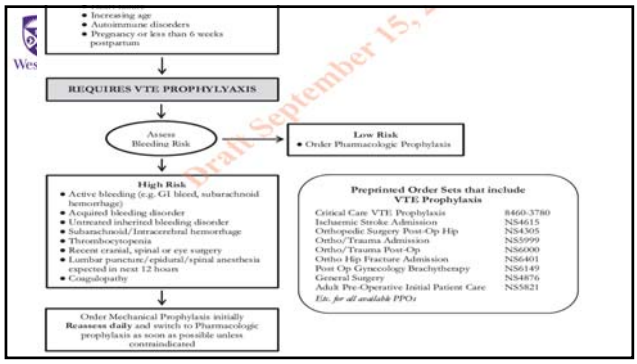

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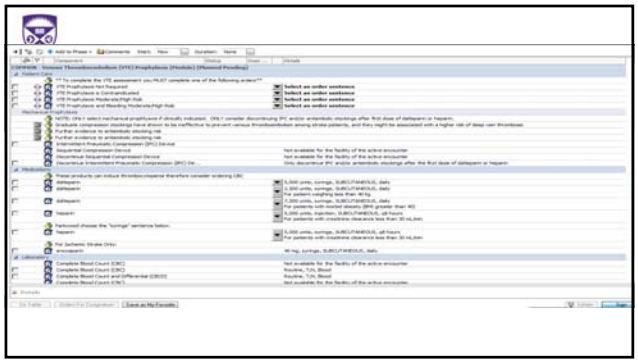

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Western

Asian venous thromboembolism guidelines: updated recommendations for the prevention of venous thromboembolism

Ngoh C. LIEW [1 *], Gina V. ALEMANY [2], Pantep ANGCHAISUKSIRI [3], Soo-Mee BANG [4], Gordon CHOI [5], Desire A. DE SILVA [6], Ji M. HONG [7], Limi LEE [8], Yong J. LI [9], Gunesan N. RAJAMONEY [9], John SUVIRAJ [10], Thiam C. TAN [11], Eric TSE [12], Li T. TEO [13], Julie VISPERAS [14], Raymond S. WONG [15], Lai H. LEE [16]

- A general assessment of VTE and bleeding risk is recommended prior to initiation of VTE prophylaxis in ischemic and hemorrhagic stroke patients
- We recommend against the use of GCS in both ischemic and hemorrhagic stroke patients
- VTE prophylaxis options for ischemic stroke patients are IPC use or pharmacological regimens with SC LMWH
- IPC is recommended for hemorrhagic stroke patients.

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Conclusions

- VTE is a frequent complication in medical and stroke patients
  - Validated in many populations
- Anticoagulant prophylaxis is indicated in most patients
- Considerations for alternative strategies in high risk patients
- Strategies for implementation are necessary

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