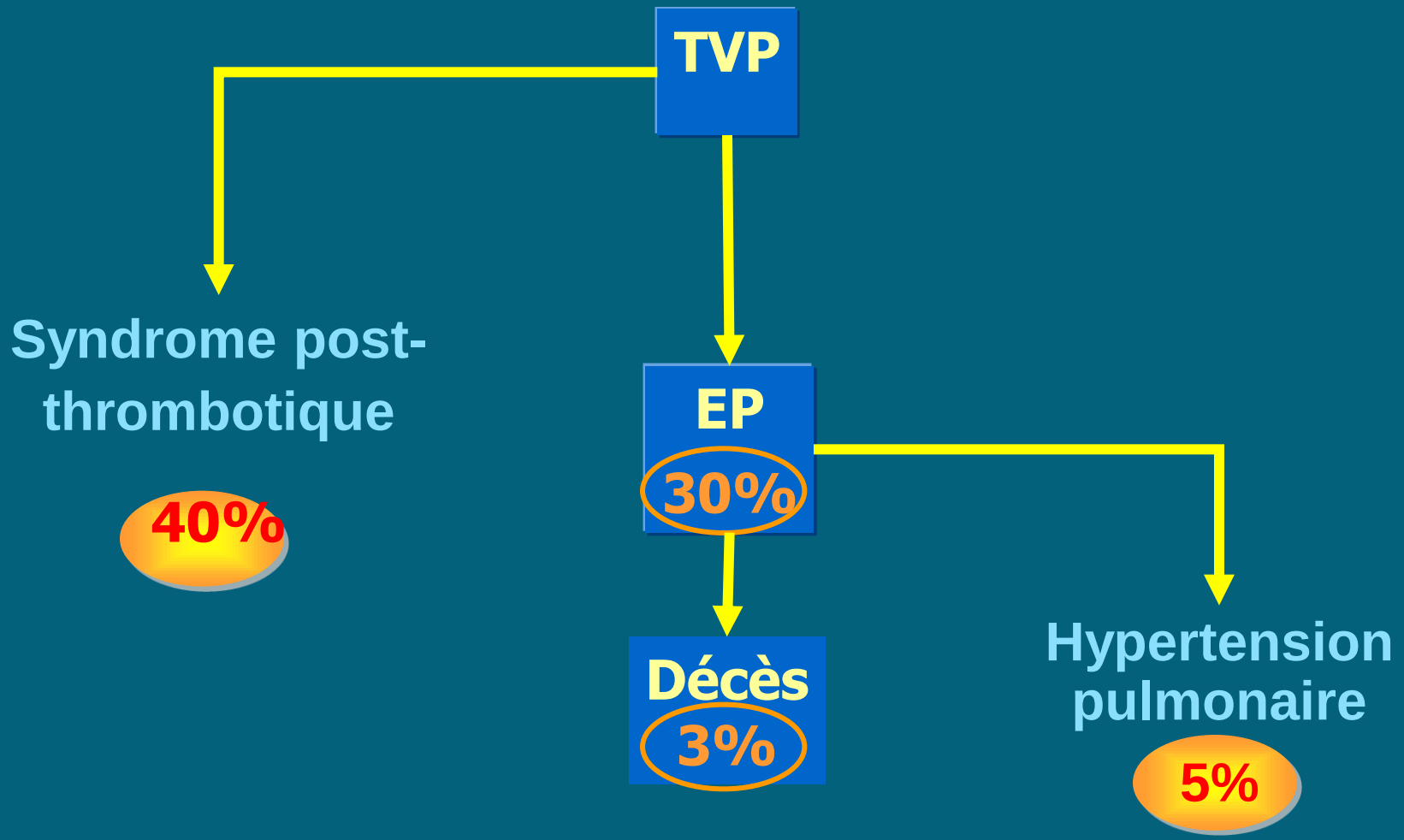
PREVENTION OF VTE IN CRITICALLY ILL PATIENTS

PR Zouheir Jerbi
Service Urggences-Réanimation
Hôpital Habib Thameur Tunis
zouheir.jerbi @rns.tn

Le fardeau de la maladie TE veineuse



[1]Brandjes DP et al. Lancet 1997;349:759-62
[2]Kahn SR et al. J Gen Intern Med 2000;26:425-9
[3]Hirsh J & Hoak J. Circulation 1996;93:2212-45
[4]Peng et al. NEJM 2004;350:2257-64

EPIDEMIOLOGY

- **Incidence of VT in the general population is not known.**
- **2 Swedish studies :**
  - **I of confirmed VT in the city of Malmô 1.6‰ inh/year (1)**
  - **Longitudinal study in Gôteborg 1.8‰ inh/year (2)**

1. Norelstrom M. J Intern Med 1992;232:155-60
2. Hanson PO Arch Intern Med 1997;157:1665-70.

Bouée et al. Thrombosis Journal (2016) 14:4
DOI 10.1186/s12959-016-0078-0

Thrombosis Journal

ORIGINAL BASIC RESEARCH Open Access

Incidence of venous thromboembolism in France: a retrospective analysis of a national insurance claims database

Stéphane Bouée[1*], Corinne Emery[1], Adeline Samson[2,3], Julie Gourmelen[4], Cécile Bailly[3] and François-Emery Cotté[3]

mortality rate were also estimated over a 12-month follow-up period.

Results: The estimated annual incidence of VTE in France was 184.0 *per* 100 000 subjects, corresponding to a total of 119 670 events countrywide. The estimated incidence of DVT and PE were respectively 119.8 and 64.2 *per* 100 000 subjects. Annual recurrence of VTE was reported in 5.5 % ($n = 99$) patients, with a significantly higher recurrence rate in patients with PE than those with DVT ($p = 0.02$). Overall, 6.2 % ($n = 112$) of patients had died over the 12-month follow-up (respectively 10.2 and 7.7 % of patients with DVT and PE).

EPIDEMIOLOGY

- Paucity of c.c. specific data
- Risks of VTE in other patient groups (surgical, trauma, medical patients) are well established and are relevant to C.I. [1,2]
- In Systematic Review Attia[3] objectively confirmed DVT rates were in the range of 10 to 80% for patients admitted to ICU or following trauma, neurosurgery or special cord injury.

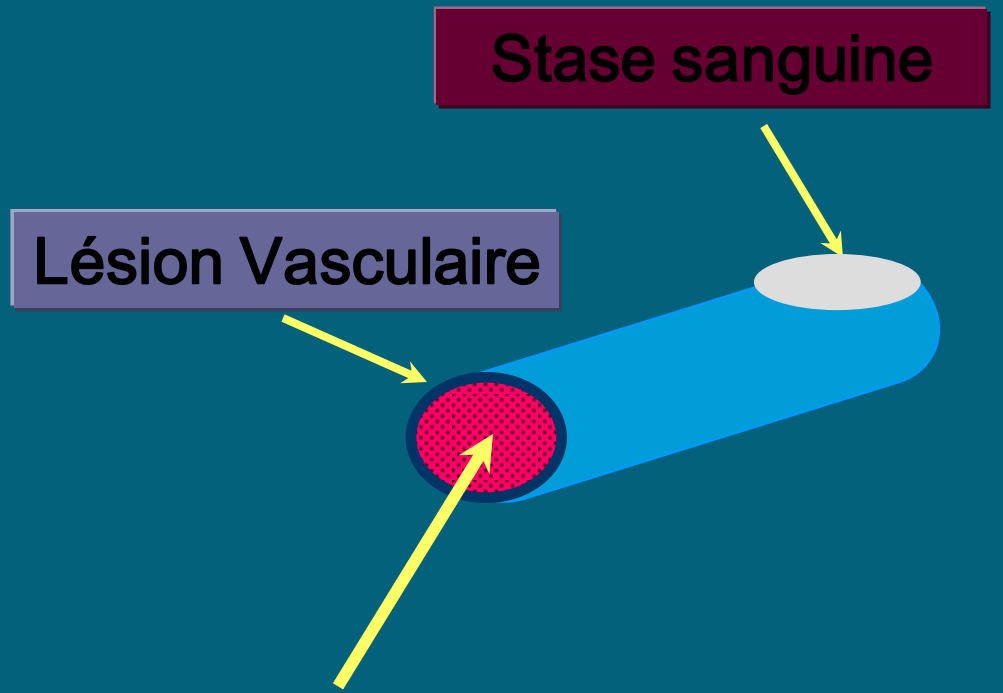
1. Chest 2001;119(suppl):1325-1755
2. J Crit Care 2002;17:95-104
3. Arch Intern Med 2001;161:1268-79

Frequency of DVT in trauma, surgery and medical patients in the absence of prophylaxis*

* Nicolaides et al International Angiology 2006:25(2):101-161

Patient Groups	No. of Studies	No. of Patients	% DVT incidence (Weighted mean)	95% CI
Stroke	9	395	56	51% to 61%
Elective Hip Replacement	17	851	51	48% to 54%
Multiple Trauma	4	536	43	39% to 47%
Total Knee Replacement	7	541	47	42% to 51%
Hip Fracture	15	805	44	40% to 47%
Spinal Cord Injury	9	458	35	31% to 39%
Retropubic Prostatectomy	8	335	32	27% to 37%
Transurethral Prostatectomy	3	150	9	5% to 15%
Patients in ICU	3	178	25	19% to 32%
General Surgery	54	4310	25	24% to 26%
Neurosurgery	5	280	22	17% to 27%
Gynecological Surgery Malignancy	4	297	22	17% to 26%
Myocardial Infarction	4	180	22	16% to 28%
Abdominal Vascular Surgery	6	258	19	15% to 25%
Peripheral Vascular Reconstruction	3	102	15	9% to 23%
Isolated Lower Limb Injuries	6	684	17	15% to 20%
Gynecological Surgery Benign Disease	4	460	14	11% to 17%
Elective Spinal Surgery	2	151	15	10% to 22%
General Medical	8	1026	12	10% to 14%
Burns	3	249	12	8.6% to 16%
Geriatric	1	131	9	5% to 15%
Knee Arthroscopy	7	832	8	6% to 10%

La Triade de Virchow (1856)



Altération des constituants du sang
(hypercoagulabilité?)

VIRSHOW'S TRIADE

- **Low blood flow : STASIS**
  - **Thrombogenic substances are not washed away and diluted in the blood but tend to concentrate locally.**
  - **Circulating inhibitors of platelets or coagulation such as ATIII, do not reach the site of a developing thrombosis in sufficient quantities.**

→ compression of a proximal vein :

- **abdominal or pelvic surgery**
- **pregnancy**

→ Reduced muscular activity :

- **anesthesia, sedation, curare**
- **Prolonged immobilization**
- **Paralysis**
- **Poor peripheral perfusion : CHF, surgery, trauma**

VIRSHOW'S TRIADE

- **Altered vessel wall :**
  - **Turbulent blood flow**
  - **Perturbation of the fibrinolytic system**
  - **Decrease of production of prostacyclin**
    - → **Surgery**
    - → **Trauma**
    - → **CV KT**

VIRSHOW'S TRIADE

- **Hypercoagulability :**
  - **Activation of coagulation throughout the circulation**
  - **Increase in the number and activity of platelets**

→ Surgery

→ Trauma

→ cancer

→ Sepsis

FICHE D'EVALUATION DU RISQUE THROMBOEMBOLIQUE :*

Etablissement : /_____/ Service : /_____

Sexe : /__/ (M/F) Age /__/__/ ans Poids /__/__/__/__/ Kg

Date de l'admission : _____ Motif d'hospitalisation : _____

VEUILLEZ COCHER LES REPONSES ADAPTEES :

Patient > 40ans et hospitalisation prévisible > 72 h

FACTEURS DE RISQUE PRESENTIFS	
☐ Déshydratation ☐ Polyglobulie/ thrombocytémie Baisn ☐ Varicose /oedème ☐ Antécédents familiaux de MTEV ☐ THS ☐ Obésité IMC>30	(1)
☐ Age >65 years ☐ Grossesse ☐ Contraception orale ☐ Syndrome néphrotique ☐ Syndrome myéloprolifératif ☐ Maladie de Behçet ☐ Post partum < 1 mois	(2)
☐ Thrombophilie ☐ Antécédents personnels de MTEV ☐ Cancer actif	(3)

FACTEURS DE RISQUE EXPOSE	
☐ Infections/ Maladie inflammatoire sans immobilisation ☐ Injection de vasoactifs sur cathéter central ou port cathéter	(1)
☐ Etat ☐ Décompensation respiratoire aigue sans ventilation ☐ Sepsis / Tuberculose ☐ Infections/ maladie inflammatoire aigue avec immobilisation	(2)
☐ AVC Ischémique avec parésie ☐ Insuffisance cardiaque NYHA III + IV ☐ Insuffisance respiratoire aigue	(3)

Score total du risque : /__/__/

SCORE TOTAL ≥ 3pt : Risque élevé

Précautions d'emploi de la prescription :

Si l'une des cases est cochée, un héparinoïde/ antiagrégant peut ne pas être indiqué. Envisager d'autres mesures préventives

☐ Présence d'un saignement actif ☐ Numération plaquettaire < 100 000 /mm3 ☐ Traitement par AINS, dipyridamol, salicylés	☐ ATCD/ de thrombopénie induite par l'héparine ☐ Anomalie de la clairance de la Créatinine : veuillez indiquer la valeur : _____

PROPHYLAXIE PRESCRITE : Aucune ☐ Mécanique ☐ Anticoagulants ☐

Produit: _____ Dose: _____ Durée : _____ (jours)

Cachet et signature du médecin **(date du scoring):**

Score actualisé : /__/__/ date : /__/__/__/

*Adapté de la fiche DERTEM : Lutz L, et al. Med Prat. 2002;52:231-234

Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study

*Alexander T Cohen, Victor F Tapson, Jean-Francois Bergmann, Samuel Z Goldhaber, Ajay K Kakkar, Bruno Deslandes, Wei Huang, Maksim Zayaruzny, Leigh Emery, Frederick A Anderson Jr, for the ENDORSE Investigators**

Summary

Background Information about the variation in the risk for venous thromboembolism (VTE) and in prophylaxis practices around the world is scarce. The ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) study is a multinational cross-sectional survey designed to assess the prevalence of VTE risk in the acute hospital care setting, and to determine the proportion of at-risk patients who receive effective prophylaxis.

Methods All hospital inpatients aged 40 years or over admitted to a medical ward, or those aged 18 years or over admitted to a surgical ward, in 358 hospitals across 32 countries were assessed for risk of VTE on the basis of hospital chart review. The 2004 American College of Chest Physicians (ACCP) evidence-based consensus guidelines were used to assess VTE risk and to determine whether patients were receiving recommended prophylaxis.

Lancet 2008; 371: 387–94

See Comment page 361

*Members listed at end of paper

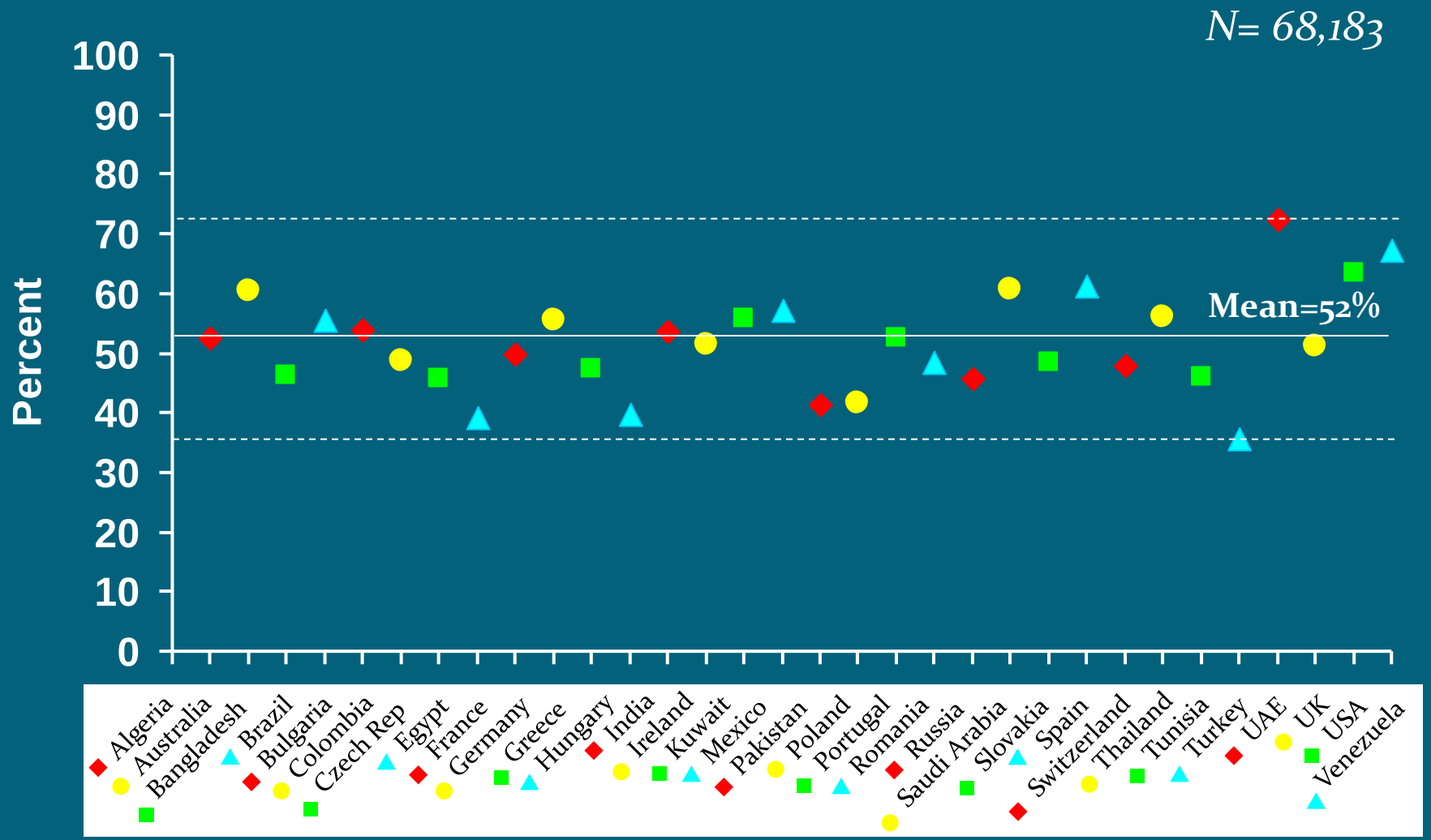
King's College Hospital, London, UK (A T Cohen MD); Duke University Medical Center, Durham, NC, USA (V F Tapson MD); Hôpital Lariboisière, University Paris 7, Paris, France (Prof J-F Bergmann MD); Brigham and Women's Hospital, Harvard Medical

A worldwide study

32 countries -- 358 hospitals

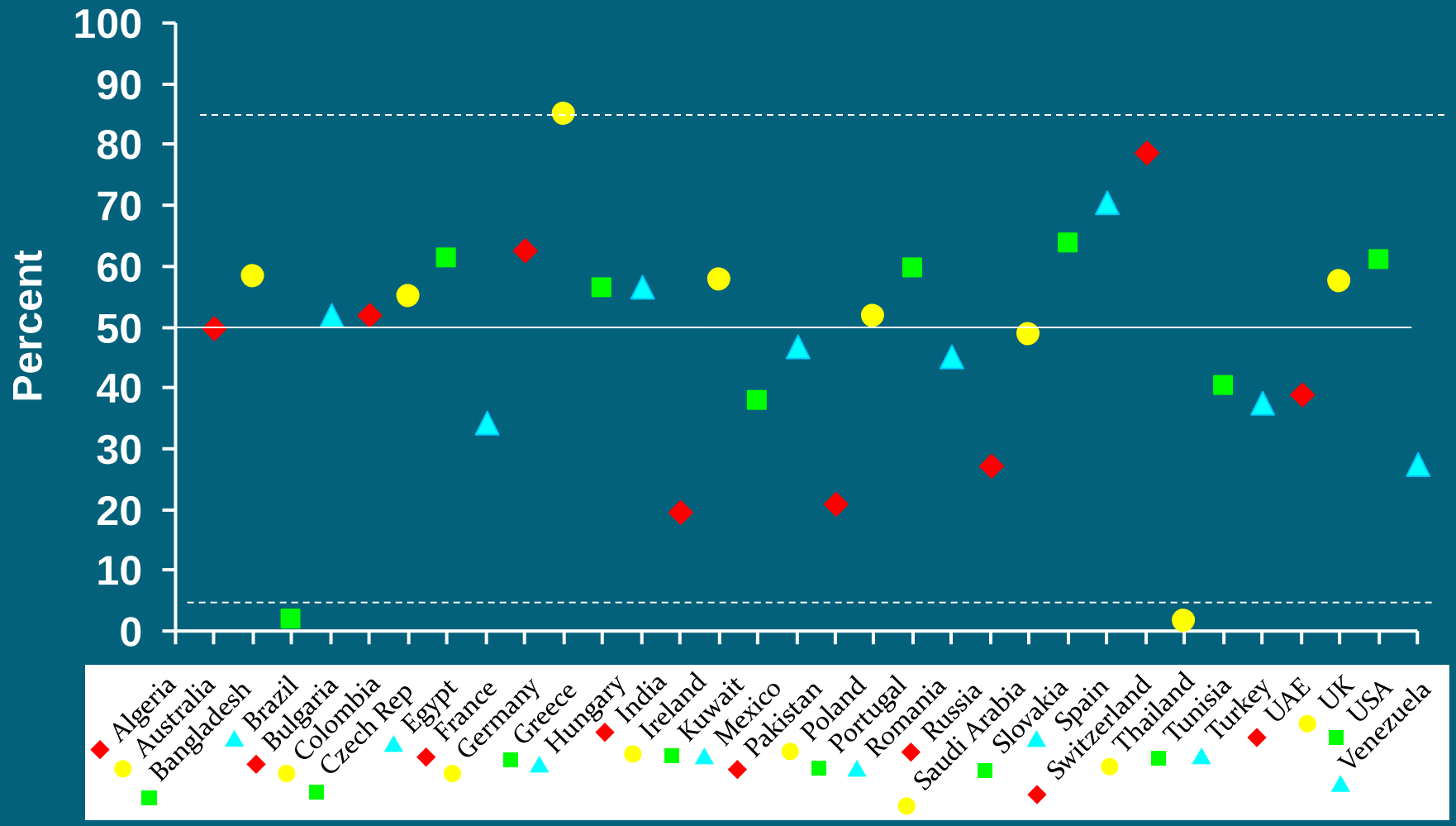
First patient enrolled August 2, 2006
Last patient enrolled January 4, 2007
Median of 8 days to enroll eligible patients/hospital

Patients at risk for VTE by country



52% at risk for VTE

ACCP recommended prophylaxis by country in patients at risk for VTE



50% received VTE prophylaxis

Venous thromboembolism risk and prophylaxis in the acute hospital care setting-results of the Endorse study in Tunisia

Zouheir Jerbi[1,6], Mohamed H. Houman[2,6], Habib Ghedira[3,6], Samir Kamoun [4,7], Afif Ben Salah [5,6]

1/ Hôpital Habib Thameur Tunis, Tunis El Manar University - 2/ Hôpital La Rabta Tunis, Tunis El Manar University - 3/ Hôpital Abderhmen Mami. Ariana, Tunis El Manar University - 4/ Hôpital Hédi Chaker. Sfax, University of Sfax - 5/ Institut Pasteur. Tunis, Tunis El Manar University - 6/Faculty of Medicine of Tunis. Tunisia, Tunis El Manar University - 7/Faculty of Medicine of Sfax. University of Sfax

Z. Jerbi, M. H. Houman, H. Ghedira, S. Kamoun, A. Ben Salah

Risque et prévention de la maladie thrombo-embolique veineuse chez les malades hospitalisés, résultats tunisiens de l'étude ENDORSE

LA TUNISIE MEDICALE - 2011 ; Vol 89 (n°10) : 784 - 789

Z. Jerbi, M. H. Houman, H. Ghedira, S. Kamoun, A. Ben Salah

Venous thromboembolism risk and prophylaxis in the acute hospital care setting-results of the Endorse study in Tunisia

LA TUNISIE MEDICALE - 2011 ; Vol 89 (n°10) : 784 - 789

LA TUNISIE MEDICALE - 2011 ; Vol 89 (n°10) : 784 - 789

Results: 885 were enrolled, 212 (24%) were surgical and 673 (76%) were medical. 408 (44, 9%) judged to be at risk, 95 (44, 8%) are surgical and 313 (46, 5%) are medical. LWMH are the most used. Mechanical prophylaxis was never used.

recommended prophylaxis.

Results: 885 were enrolled, 212 (24%) were surgical and 673 (76%) were medical. 408 (44, 9%) judged to be at risk, 95 (44, 8%) are surgical and 313 (46, 5%) are medical. LWMH are the most used. Mechanical prophylaxis was never used.

Conclusion: The percentage of at risk patient in Tunisia is comparable to these of other countries. The majority of at risk patient are medical. The prophylaxis was under used. Hospital strategies to assess patient VTE risk and implementation of prophylaxis protocols are needed.

Other Conditions present DURING hospital admission			
Acute heart failure (NYHA Class III or IV)	1 (1.1%)	45 (14.4%)	46 (11.3%)
Ischemic stroke	1 (1.1%)	1 (0.3%)	2 (0.5%)
Hemorrhagic stroke	1 (1.1%)	2 (0.6%)	3 (0.7%)
Other cardiovascular	12 (12.6%)	80 (25.6%)	92 (22.5%)
Other medical condition	8 (8.4%)	14 (4.0%)	22(5.4%)
Admitted to ICU/CCU	34 (35.8%)	86 (27.5%)	120 (29.4%)
Central venous catheter	9 (9.5%)	11 (3.5%)	20 (4.9%)
Mechanical ventilation	5 (5.3%)	6 (1.9%)	11 (2.7%)
Immobile with bathroom privileges	13 (13.7%)	91 (29.1%)	104 (25.5%)
Complete immobilization	44 (46.3%)	25 (8.0%)	69 (16.9%)
Cancer therapy	2 (2.1%)	5 (1.6%)	7 (1.7%)
Heparin induced	0 (0.0%)	0 (0.0%)	0 (0.0%)
NSAID on admission (excluding aspirin)	0 (0.0%)	11 (3.5%)	11 (2.7%)

The most common contraindication to pharmacological prophylaxis (Table4) is bleeding at hospital admission (4.5%) in medical patients and (4.2%) in surgical patients. 25 (8.0%) of at risk medical patients and 10 (10.5%) of at risk surgical patients were considered to have a high bleeding risk, sufficient to present a contraindication to pharmacological prophylaxis.

167 (41, 0%) patients deemed to be at risk for VTE received ACCP-recommended types of prophylaxis, of whom 92 (29,4%) were medical patients and 74 (79%) were surgical patients. The rate of prophylaxis is low even in medical patients with high risk such as congestive heart failure (22%) and

following radical prostatectomy.[15] Neurosurgeons have used compression boots plus fixed low dose heparin in craniotomy patients with malignancies.[16]

Attempting to change the status quo in the ICU forces physicians to face challenges that are particular to those previously mentioned groups of patients. First, the efficacy of various prophylaxis modalities has rarely been studied in this population. Therefore, there does not exist the same literature-based evidence for implementing prophylaxis in this setting compared with others. Second, these patients are often bleeding overtly or are admitted with thrombocytopenia. Accordingly, heparin or warfarin are often contraindicated. Third, these patients may have leg ulcers, wounds, or peripheral arterial occlusive disease that preclude the use of intermittent pneumatic compression devices. With these prob-

lems in mind, it is useful to examine the current state of prophylaxis used for ICU patients.

In 1994, the Venous Thromboembolism Research Group published a study[17] in which we found that at

join clinical trials to enhance our knowledge in this last frontier of PE and DVT prevention.

Samuel Z. Goldhaber, MD, FCCP
Boston

THROMBOPROPHYLAXIS IN CRITICALLY ILL PATIENTS

		Intervention		DVT No/ Total Patients (%)	
Source	Method of Diagnosis	Control	Experimental	Control	experimental
Cade[31] (1982)	Fg LS for 4-10d	Placebo	Heparin,5000U SC bid	NR/NR(29)	NR:NR(13)
Kapoor et al[32] (1999)	DUS on admission and every 3 d	Placebo	Heparin,5000U SC bid	122/390(31)	44/401(11)
Fraisse et al[28]	Venography befor day 21	Placebo	Nadroparin, approximately 70AXa U/kgSCqd	24/85 (28)	13/84 (15)

1. Crit Care Med 1982;10:448-50
2. Crit Care Med 1999;27(suppl):A69
3. Am J Resp Crit Care Med 2000;161:1109-14

ORIGINAL ARTICLE

Dalteparin versus Unfractionated Heparin in Critically Ill Patients

The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group

RESULTS

There was no significant between-group difference in the rate of proximal leg deep-vein thrombosis, which occurred in 96 of 1873 patients (5.1%) receiving dalteparin versus 109 of 1873 patients (5.8%) receiving unfractionated heparin (hazard ratio in the dalteparin group, 0.92; 95% confidence interval [CI], 0.68 to 1.23; P=0.57). The proportion of patients with pulmonary emboli was significantly lower with dalteparin (24 patients, 1.3%) than with unfractionated heparin (43 patients, 2.3%) (hazard ratio, 0.51; 95% CI, 0.30 to 0.88; P=0.01). There was no significant between-group difference in the rates of major bleeding (hazard ratio, 1.00; 95% CI, 0.75 to 1.34; P=0.98) or death in the hospital (hazard ratio, 0.92; 95% CI, 0.80 to 1.05; P=0.21). In prespecified per-protocol analyses, the results were similar to those of the main analyses, but fewer patients receiving dalteparin had heparin-induced thrombocytopenia (hazard ratio, 0.27; 95% CI, 0.08 to 0.98; P=0.046).

CONCLUSIONS

Among critically ill patients, dalteparin was not superior to unfractionated heparin in decreasing the incidence of proximal deep-vein thrombosis. (Funded by the Canadian Institutes of Health Research and others; PROTECT ClinicalTrials.gov number, NCT00182143.)

MN) assume responsibility for the integrity of this article. Address reprint requests to Dr. Cook at the Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University Health Sciences Center, Rm. 2C10, 1200 Main St. W., Hamilton, ON L8N 3Z5, Canada, or at debcook@mcmaster.ca.

This article (10.1056/NEJMoa1014475) was published on March 22, 2011, at NEJM.org.

N Engl J Med 2011;364:1305-14.

Thrombo-prophylaxis in acutely ill medical and critically ill patients

Saurabh Saigal, Jai Prakash Sharma[1], Rajnish Joshi[2], Dinesh Kumar Singh

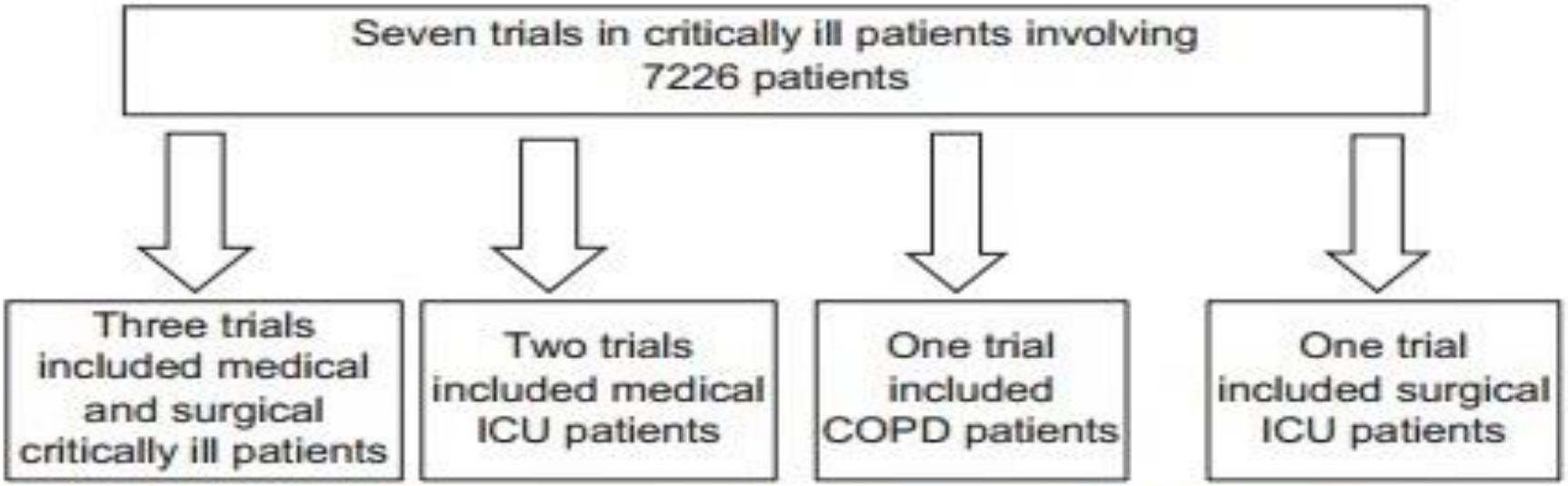


Figure 2: Schematic representation of trials in critically ill patients

Indian Journal of Critical Care Medicine June 2014 Vol 18 Issue 6

Clinical take away in critically ill patients

On the basis of the above meta-analysis, evidence to date suggests that any type of heparin thrombo-prophylaxis decreases DVT and PE in medical-surgical critically ill patients, and LMWH compared with bid UFH decreases PE and symptomatic PE. Major bleeding and mortality rates do not appear to be significantly influenced by heparin thrombo-prophylaxis in the ICU setting. No one form of heparin is superior to other as advertised by pharmaceutical companies. Meanwhile, all relevant clinical outcomes of thrombo-prophylaxis and their associated economic consequences should be considered. As well as considerations of drug availability, patient comfort, and ease of administration should guide decisions regarding thrombo-prophylaxis in critically ill patients.

Heparin Thromboprophylaxis in Medical-Surgical Critically Ill Patients: A Systematic Review and Meta-Analysis of Randomized Trials*

Waleed Alhazzani, MD[1]; Wendy Lim, MD[2]; Roman Z. Jaeschke, MD[3,4];

Conclusions: Trial evidence to date suggests that any type of heparin thromboprophylaxis decreases deep vein thrombosis and pulmonary embolism in medical-surgical critically ill patients, and low-molecular-weight heparin compared with bid unfractionated heparin decreases pulmonary embolism and symptomatic pulmonary embolism. Major bleeding and mortality rates do not appear to be significantly influenced by heparin thromboprophylaxis in the ICU setting. Trial methodology, indirectness, and the heterogeneity and imprecision of some results temper inferences from this literature. (*Crit Care Med* 2013; 41:2088–2098)

Health Research. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: debcook@mcmaster.ca

DOI: 10.1097/CCM.0b013e31828cf194

(VTE), are common preventable complications of hospitalization. Anticoagulant thromboprophylaxis, typically unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), reduces asymptomatic and symptomatic VTE in medical (1, 2) and surgical (3) patients. Medical-surgical patients in the ICU have several VTE risk factors, including

Time to Recommend Heparin and Low-Molecular-Weight Heparins in Thromboprophylaxis in Medical-Surgical Critically Ill Patients*

Nicola Volpi, PhD
Department of Life Sciences
University of Modena and Reggio Emilia
Modena, Italy

*See also p. 2088.

Key Words: heparin; intensive care unit; low-molecular-weight heparin; meta-analysis; venous thromboembolism

The author has disclosed that he does not have any potential conflicts of interest.

DOI: 10.1097/CCM.0b013e31828fd852

Critically ill patients in the medical-surgical ICU are at high risk for deep venous thrombosis (DVT) and pulmonary embolism (PE), collectively known as *venous thromboembolism* (VTE) (1), developing 13–31% of symptomatic or asymptomatic DVT in the absence of thromboprophylaxis (2). The use of anticoagulant thromboprophylaxis significantly decreases the risk of VTE in ICU patients (1, 2). However, critically ill patients are also at high risk of bleeding (3), so anticoagulant thromboprophylaxis must achieve a balance between dynamic thrombotic and bleeding risks.

8.0 Critical Care

8.1. For patients admitted to a critical care unit, we recommend routine assessment for VTE risk and routine thromboprophylaxis in most (Grade 1A).

8.2. For critical care patients who are at moderate risk for VTE (*eg*, medically ill or postoperative general surgery patients), we recommend using LMWH or LDUH thromboprophylaxis (Grade 1A).

8.3. For critical care patients who are at higher risk (*eg*, following major trauma or orthopedic surgery), we recommend LMWH thromboprophylaxis (Grade 1A).

8.4. For critical care patients who are at high risk for bleeding, we recommend the optimal use of mechanical thromboprophylaxis with GCS and/or IPC at least until the bleeding risk decreases (Grade 1A). **When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C).

RRR = relative risk reduction; SC = subcutaneous; SCI = spinal cord injury; THR = total hip replacement; TKR = total knee replacement; VFP = venous foot pump; VKA = vitamin K antagonist; VTE = venous thromboembolism

3.0 Critically Ill Patients

3.2. In critically ill patients, we suggest against routine ultrasound screening for DVT (Grade 2C).

3.4.3. For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis over no prophylaxis (Grade 2C).

3.4.4. For critically ill patients who are bleeding, or are at high risk for major bleeding, we suggest mechanical thromboprophylaxis with GCS (Grade 2C) **or IPC** (Grade 2C) **until the**

Executive Summary

CHEST 2012; 141(2)(Suppl):7S–47S

evidence, and some articles with quite extensive summary tables of primary studies. In total, this represented 600 recommendations summarized in

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Waller, MD; and COL Lisa Moores, MD, FCCP

PODCAST

BACKGROUND: We update recommendations on 12 topics that were in the 9th edition of these guidelines, and address 3 new topics.

METHODS: We generate strong (Grade 1) and weak (Grade 2) recommendations based on high- (Grade A), moderate- (Grade B), and low- (Grade C) quality evidence.

RESULTS: For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B), or edoxaban (Grade 2B) over vitamin K antagonist (VKA) therapy, and suggest VKA therapy over low-molecular-weight heparin (LMWH; Grade 2C). For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C). We have not changed recommendations for who should stop anticoagulation at 3 months or receive extended therapy. For VTE treated with anticoagulants, we recommend against an inferior vena cava filter (Grade 1B). For DVT, we suggest not using compression stockings routinely to prevent PTS (Grade 2B). For subsegmental pulmonary embolism and no proximal DVT, we suggest clinical surveillance over anticoagulation with a low risk of recurrent VTE (Grade 2C), and anticoagulation over clinical surveillance with a high risk (Grade 2C). We suggest thrombolytic therapy for pulmonary embolism with hypotension (Grade 2B), and systemic therapy over catheter-directed thrombolysis (Grade 2C). For recurrent VTE on a non-LMWH anticoagulant, we suggest LMWH (Grade 2C); for recurrent VTE on LMWH, we suggest increasing the LMWH dose (Grade 2C).

CONCLUSIONS: Of 54 recommendations included in the 30 statements, 20 were strong and none was based on high-quality evidence, highlighting the need for further research.

CHEST 2016; 149(2):315-352

KEY WORDS: antithrombotic therapy; evidence-based medicine; GRADE approach; venous

Main results

Sixteen studies with a combined total of 34,369 participants with an acute medical illness were included in this review. We identifie
10 studies comparing heparin with placebo or no treatment and six studies comparing LMWH to UFH. Just under half of the studie
had an open-label design, putting them at a risk of performance bias. Descriptions of random sequence generation and allocatio
concealment were missing in most of the studies. Heparin reduced the odds of deep vein thrombosis (DVT) (OR 0.38; 95% CI 0.29 t
0.51; P < 0.00001). The estimated reductions in symptomatic non-fatal pulmonary embolism (PE) (OR 0.46; 95% CI 0.19 to 1.10
P = 0.08), fatal PE (OR 0.71; 95% CI 0.43 to 1.15; P = 0.16) and in combined non-fatal PE and fatal PE (OR 0.65; 95% CI 0.42 t
1.00; P = 0.05) associated with heparin were imprecise. Heparin resulted in an increase in major haemorrhage (OR 1.81; 95% CI 1.1
to 2.98; P = 0.02). There was no clear evidence that heparin had an effect on all-cause mortality and thrombocytopaenia. Compare
with UFH, LMWH reduced the risk of DVT (OR 0.77; 95% CI 0.62 to 0.96; P = 0.02) and major bleeding (OR 0.43; 95% CI 0.2
to 0.83; P = 0.01). There was no clear evidence that the effects of LMWH and UFH differed for the PE outcomes, all-cause mortalit

Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction) (Review)

Authors' conclusions

The data from this review describe a reduction in the risk of DVT in patients presenting with an acute medical illness who receive heparin thromboprophylaxis. This needs to be balanced against an increase in the risk of bleeding associated with thromboprophylaxis. The analysis favoured LMWH compared with UFH, with a reduced risk of both DVT and bleeding.

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 5

http://www.thecochranelibrary.com

WILEY

Critical Care

CRITICAL CARE

Thromboprophylaxis patterns and determinants in critically ill patients: a multicenter audit

Critical Care 2014, **18**:R82 doi:10.1186/cc13844

François Lauzier (francois.lauzier@med.ulaval.ca)
John Muscedere (muscedej@kgh.kari.net)
Éric Deland (Eric.Deland@USherbrooke.ca)
Demetrios Jim Kutsogiannis (jim.kutsogiannis@ualberta.ca)

Results

We enrolled 1,935 patients (62.3 ± 16.7 years, Acute Physiology and Chronic Health Evaluation [APACHE] II score 19.1 ± 8.3). Patients received thromboprophylaxis with unfractionated heparin (UFH) (54.0%) or LMWH (27.6%). Guideline concordance occurred for 95.5% patient-days and was more likely in patients who were sicker (odds ratio (OR) 1.49, 95% confidence interval (CI) 1.17, 1.75 per 10-point increase in APACHE II), heavier (OR 1.32, 95%CI 1.05, 1.65 per 10-m/kg^2 increase in body mass index), had cancer (OR 3.22, 95%CI 1.81, 5.72), previous venous thromboembolism (OR 3.94, 95%CI 1.46,10.66), and received mechanical ventilation (OR 1.83, 95%CI 1.32,2.52). Reasons for not receiving thromboprophylaxis were high risk of bleeding (44.5%), current bleeding (16.3%), no reason (12.9%), recent or upcoming invasive procedure (10.2%), nighttime admission or discharge (9.7%), and life-support limitation (6.9%). LMWH was less often administered to sicker patients (OR 0.65, 95%CI 0.48, 0.89 per 10-point increase in APACHE II), surgical patients (OR 0.41, 95%CI 0.24, 0.72), those receiving vasoactive drugs (OR 0.47, 95%CI 0.35, 0.64) or renal replacement therapy (OR 0.10, 95%CI 0.05, 0.23).

Conclusions

Guideline concordance for thromboprophylaxis was high, but LMWH was less commonly used, especially in patients who were sicker, had surgery, or received vasopressors or renal replacement therapy, representing a potential quality improvement target.

PHARMACOLOGICAL PROPHYLAXIS

- unfractionated (Low-dose) Heparin (LDUFH)

  (5000UI sc bid/ Tid)
- Low molecular-weigh heparins (LMWH)
- Other products :
  - Penta saccharide
  - NOAC

Robinson et al. Critical Care 2013, 17:R25
http://ccforum.com/content/17/2/R25

CRITICAL CARE

RESEARCH Open Access

A comparative study of varying doses of enoxaparin for thromboprophylaxis in critically ill patients: a double-blinded, randomised controlled trial

Sian Robinson[1*], Aleksander Zincuk[1], Ulla Lei Larsen[1], Claus Ekstrøm[2], Mads Nybo[3], Bjarne Rasmussen[4] and Palle Toft[1]

Conclusions: Doses of 40 mg QD enoxaparin (Europe) or 30 mg BID (North America) yield levels of anti-Xa which may be inadequate for critically ill patients. A weight-based dose yielded the best anti-Xa levels without bioaccumulation, and allowed the establishment of near steady-state levels from the first day of enoxaparin administration.

and 0.15 IU/ml were achieved with doses of 40 mg QD and 30 mg BID respectively. This increased significantly to 0.33 IU/ml and 0.40 IU/ml for doses of 40 mg BID and 1 mg/kg QD respectively. Thus anti-Xa response profiles differed significantly over the three days between enoxaparin treatment groups ($P < 0.0001$). Doses of 40 mg BID and1 mg/kg QD enoxaparin yielded target anti-Xa levels for over 80% of the study period. There were no adverse effects.

Conclusions: Doses of 40 mg QD enoxaparin (Europe) or 30 mg BID (North America) yield levels of anti-Xa which may be inadequate for critically ill patients. A weight-based dose yielded the best anti-Xa levels without bioaccumulation, and allowed the establishment of near steady-state levels from the first day of enoxaparin administration.

Trial registration: Current Controlled Trials ISRCTN91570009.

Results: Median peak (= 4 hours post administration) aFXa levels increased significantly with an increase in enoxaparin dose, from: 0.13 IU/ml at 40 mg, to 0.14 IU/ml at 50 mg, 0.27 IU/ml at 60 mg and 0.29 IU/ml at 70 mg respectively (P = 0.002*) . At 12 hours post administration, median aFXa levels were still within therapeutic range for those patients who received 60 mg (P= 0.02*).

Conclusions: Our study confirmed that a standard dose of 40 mg enoxaparin yielded sub-therapeutic levels of aFXa in critically ill patients. Higher doses resulted in better peak aFXa levels with a ceiling effect observed at 60 mg. The present study seems to suggest inadequate dosage as one of the possible mechanisms for the higher failure rate of enoxaparin in ICU patients.

Torben Bjerregaard Larsen (tblarsen@dadlnet.dk)
Bjarne Rasmussen (bjarne.rasmussen@ouh.regionsyddanmark.dk)
Palle Toft (palle.toft@ouh.fyns-amt.dk)

oped in 9 of 138 patients (5.1%; 95% CI, 2.5–10.1). In summary, daily dalteparin 5000 IU did not appear to bioaccumulate or to be associated with excess bleeding in this cohort of critically ill patients with severe renal insufficiency. This observation is supported by a systematic review that found that, when used a prophylactic doses, LMWH failed to bioaccumulate even when administered to patients with end-stage renal disease who were not necessarily critically ill (31).

In summary, ICU patients with renal insufficiency are at high risk for VTE and bleeding. Although therapeutic doses of LMWH may bioaccumulate over time, it does not appear that bioaccumulation of prophylactic doses of LMWH occurs.

high risk for venous thromboembolism, and the morbidity and mor- illness

Failure of Anticoagulant Thromboprophylaxis: Risk Factors in Medical-Surgical Critically Ill Patients*

Wendy Lim, MD[1]; Maureen Meade, MD[1,2]; Francois Lauzier, MD[3,4]; Ryan Zarychanski, MD[5,6]; Sangeeta Mehta, MD[7]; Francois Lamontagne, MD[8]; Peter Dodek, MD[9]; Lauralyn McIntyre, MD[10]; Richard Hall, MD[11,12]; Diane Heels-Ansdell, MSc[2]; Robert Fowler, MD[7]; Menaka Pai, MD[1]; Gordon Guyatt, MD[1,2]; Mark A. Crowther, MD[1,13]; Theodore E. Warkentin, MD[1,13]; P. J. Devereaux, MD[1,2]; Stephen D. Walter, PhD[2]; John Muscedere, MD[14]; Margaret Herridge, MD[7]; Alexis F. Turgeon, MD[3,15]; William Geerts, MD[16]; Simon Finfer, MD[17,18]; Michael Jacka, MD[19,20]; Otavio Berwanger, MD[21]; Marlies Ostermann, MD[22]; Ismael Qushmaq, MD[23]; Jan O. Friedrich, MD[7]; Deborah J. Cook, MD[1,2]; for the PROphylaxis for ThromboEmbolism in Critical Care Trial Investigators, the Canadian Critical Care Trials Group, and the Australian and New Zealand Intensive Care Society Clinical Trials Group

Conclusions: Failure of standard thromboprophylaxis using low molecular-weight heparin or unfractionated heparin is more like in ICU patients with elevated body mass index, those with a pe sonal or family history of venous thromboembolism, and thos receiving vasopressors. Alternate management or incremental risk reduction strategies may be needed in such patients. (*Crit Care Med* 2015; 43:401–410)

Key Words:

on intensive care unit admission, and the incidence was 9.6% (95% confidence interval 6.3–13.8) over the intensive care unit stay. We identified four independent risk factors for intensive care unit-acquired deep venous thrombosis: personal or family history of venous thromboembolism (hazard ratio 4.0, 95% confidence interval 1.5–10.3), end-stage renal failure (hazard ratio 3.7, 95% confidence interval 1.2–11.1), platelet transfusion (hazard ratio 3.2, 95% confidence interval 1.2–8.4), and vasopressor use (hazard ratio 2.8, 95% confidence interval 1.1–7.2). Patients with deep venous thrombosis had a longer duration of mechanical ventilation ($p = .03$), intensive care unit stay ($p = .005$), and hospitalization ($p < .001$) than patients without deep venous thrombosis.

Deep venous thrombosis in medical-surgical critically ill patients: Prevalence, incidence, and risk factors

Deborah Cook, MD
David Schiff, MD;
th, MSc;

Despite universal thromboprophylaxis, medical-surgical critically ill patients remain at risk for lower extremity deep venous thrombosis.

Objective: Critically
thromboembolism. The
incidence, and risk facto
thrombosis among critic
Design: Prospective
Setting: Closed univ
Patients: We enroll
expected to be in int
criteria were an admit
gery, pregnancy, and li
Interventions: Interv
compression ultrasound
sion, twice weekly, and
suspected. Thromboprop
We recorded deep venous thrombosis risk factors at baseline and daily, using multivariate regression analysis to determine independent predictors. Patients were followed to hospital discharge.

Results: Among 261 patients with a mean Acute Physiology and Chronic Health Evaluation II score of 25.5 (±8.4), the prevalence of deep venous thrombosis was 2.7% (95% confidence interval 1.1–5.5)

e was 9.6% (95%
are unit stay. We
sive care unit-ac-
history of venous
nce interval 1.5–
95% confidence
io 3.2, 95% confi-
ard ratio 2.8, 95%
enous thrombosis
= .03), intensive
001) than patients

hylaxis, medical-surgical critically ill patients remain at risk for lower extremity deep venous thrombosis. Further research is needed to evaluate the risks and benefits of more intense venous thromboembolism prophylaxis. (Crit Care Med 2005; 33:1565–1571)

KEY WORDS: critical care; deep venous thrombosis; prevalence; incidence; risk factors

Is It Time for Individualized Thromboprophylaxis Regimens in the ICU?*

Ian Welsby, BSc, MBBS, FRCA
Department of Anesthesiology
Duke University Medical Center
Durham, NC

Thomas L. Ortel, MD, PhD
Department of Medicine
Duke University Medical Center
Durham, NC

for either endpoint, the latter being complicated by the multiple factors contributing to mortality risk in this population.

These findings, both from PROTECT and the current analysis, are important. They support the use of the LMWH dalteparin as a once daily dosing to match UFH in preventing VTE and reducing the prevalence of PE. From a safety standpoint, major (5%) or any (13%) bleeding was similar in UFH and LMWH groups. Bleeding with LMWH is often a clinical concern given only partial reversibility with protamine and renal

In summary, focusing efforts on safely achieving effective antithrombotic levels using novel regimens and/or monitoring techniques, and evaluating combined thromboprophylactic modalities, are essential components of strategies to prevent VTE in the critically ill. One size is unlikely to fit all.

dose

- Perturbation of renal fonction : no bioaccumulation 1
- Fuster-Lulch and colleagues reported that30% of patients show augmented renal clearence during the first week of critical illness

  (post-operative, sepsis, trauma)2
- LMWH in elderly patients with impaired renal fonction, Enoxaparin but not Tinzaparin accumulated over 8 days3
- The pharmacokinetics of different LWMH varies 3,4

/ Robinson S. and all crit care 2010; 14:R41
2/ Aneasth intensive care 2008; 36: 674-680
3/Mahe I; and all.Thromb heamost 2007; 97;5861-586
4/ Sammama MM. And all. Semin thromb heamost 2000; suppl 1: 31-38

Mechanical thromboprophylaxis in critically ill patient systematic review and meta-analysis*

21 relevant studies : 5 randomised trial: 811 patients

13 observational studies : 3421 patients

3 surveys

Conclusion: Until large RCT are conducted, the role of mechanical approches to thromboprophylaxis for intensive care patients remains uncertain.

*Limpus A, Am J Crit Care 2006 Jul;15(4):402-10

ELECTRONIC ALERTS TO PREVENT VTE AMONG HOSPITALZED PATIENTS

- **A computer program Linked to the patient database Patient at risk of DVT**
  - **1255 the physician was alerted to a patient's risk**
  - **1251 control (end point confirmed DVT or PE 90 days)**

	Intervention gr	Control gr
MP	10%	1.5% P<0.001
PP	23.6%	13% P<0.001
End point	4.9%	8.2%

→ **Computer alert reduced the R of DVT or PE at 90 days by 41% (hazad R 0.59, 95% confidence interv 0.43 to P = 0.001**

N Engl J Med 2005;352:969-77

THROMBOPROPHYLAXIS IN CI

- **Critical Analysis of patient Safety Practices (1)**

✓ **79 patient safety interventions based on the strength of the evidence supporting more wide spread implementation of these procedures**

✓ **Highest ranked :**

✓ **« appropriate use of prophylaxis to prevent VTE in patient at risk »**

- ✓ **Thromboprophylaxis :**
  - ↙ **adverse patient outcomes**
  - ↙ **overall costs**

1. Agency for Health Care Rescarch and Quality July 2001 www.ahrq.gov/Clinic/ptsafety

- Critically Ill Patients are at high risk
- Thromboprophylaxis
- Daily challenge (VTE risk/ bleeding risk)
- UFH or LWMH
- Which dose
- Subcutaneously (vasopressor)
- Renal insufficiency
- Mechanical thromboprophylaxis :IPC / CGS
- MP+PP
- NOAC
- Individulise thromboprophylaxis (Obese, VTE history, vasopressor,...)