Travel-Related Thrombosis

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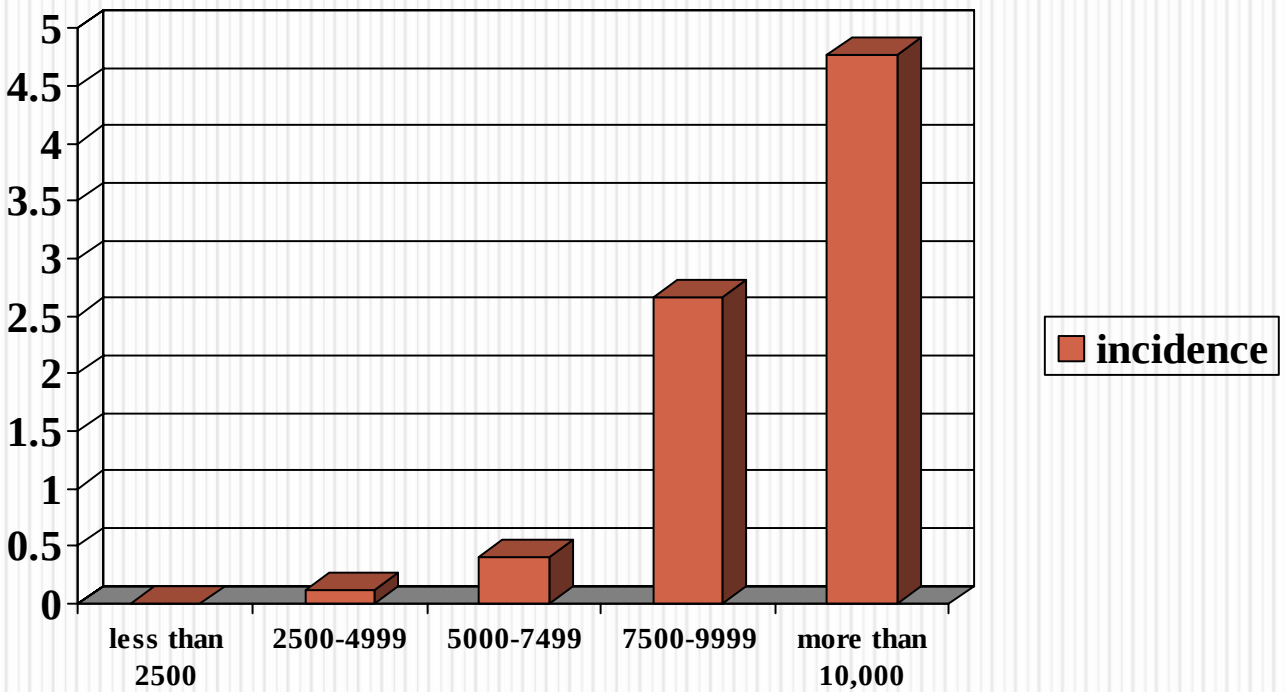
Incidence of PE According to Distance Traveled by Air

Incidence of Pulmonary embolism(per million Passenger arrivals)



Frequency of PE increased 150 fold in long haul travelers >5000km compared to <5000km

Lapostolle N Engl J Med, 2001

Risk Factors

Risk Factor	No. of patients
High Risk	4
Immobilization more than 3 days	1
Recent surgery(within past 3 weeks)	1
Multiple trauma	0
Previous DVT or PE	3
Cancer	1
Pregnancy or postpartum period	0
Heart failure	2
Coagulation disorder	0
Moderate risk	49
Varicose veins	14
Estrogen or progesterone treatment	**18**
Age more than 40 years	**49**
Obesity	5
Tobacco use	4
Nephrotic syndrome	0

Lapostolle N Engl J Med, 2001

WHO Recommendations
(March 2001)

- Multicenter epidemiological studies should be performed.
- Studies in volunteers to examine environmental and behavioral aspects.
- An interventional prospective study should be carried out.

Venous Thrombosis after Long Travel (>8hr) Flights

	Passengers	Controls	RR	95% CI
No’	964	1213		
ICMVT	2.1%	0.8%	2.52	1.2-5.26
DVT	0.7%	0.2%	4.40	1.04-18.6
Total	2.8%	1.0%	2.83	1.46-5.49

Schwartz, Arch Intern Med, 2003

Problem Estimation

300 million long flights travelers yearly

2% asymptomatic DVT → 6 million

10% symptomatic DVT → 600,000

30% Pulmonary embolism → 200,000

10% fatal PE → 20,000

Presentation

Site:

* Superficial
* Sinus vein
* Pulmonary embolism
* Upper extremity
* Isolated calf muscle
* Deep vein legs

Timing

* Usually within 2 weeks
* Median 4 days
* Up to 1 month

Predisposing Factors (1)

A) Cabin related

- Cramped sitting position
- More in economy class
- 83% Non-aisle seats
- Lower air pressure, relative hypoxia
- Low humidity and dehydration
- Some features differ among airlines

Predisposing Factors (2)

B) Passenger related

- Age over 40
- Previous VTE
- Thrombophilia
- Hormonal Therapy
- Pregnancy
- Varicose veins
- Cancer
- Overweight

Gender and Travel-Related PE

- Travelers who experienced PE after landing in CDG - 90/116 (78%) were females.
- Risk: 3.5 folds higher in females.

Lapostolle Thromb Haemost, 2009

Meta-analysis of Travel-Related Thrombosis

- 14 studies (11 case-control, 2 cohort, 1 case-crossover) 4055 cases of VTE.
- Overall relative risk 2.0
- 18% increase of VTE risk by every 2 hours of travel (26% for air travel).

Chandra Ann Intern Med, 2009

The MEGA Study

- Patients younger than 70y with a first VTE.
- 1906 patients: 233 traveled ≥4 h within 8 weeks.
- Travel increased risk by 2 folds. (95% CI 1.5-3.0).
- No difference by mode of travel.
- Oral contraceptives: estimated OR-20
- Factor V Leiden (OR 8; 95% CI 2.7-24.7)
- BMI > 30kg/m (OR 9.9; 95% CI 3.6-27.6)
- Height > 190cm (OR 4.7; 95% CI 1.4-15.4)
- Height < 160cm (OR 4.9; 95% CI 0.9-25.6)

Cannegieter PLoS Med, 2006

Frankfurt Airport Hospital

- 257 PE patients - 62 were travelers (24%)
- In travelers – PE was associated with more severe presentations but long-term outcome was good.

Lehmain Eur Heart J, 2009

The Need for a Registry

- Information on prolonged travel and VTE in real life is somewhat limited.
- VTE registries can be helpful in this regard.
- RIETE is an ongoing, multicenter, international observational registry on patients with VTE.

Characteristics of Patients with a Recent Travel History and Other Patients in the Registry [1]

	Recent Travelers	Other Patients in Registry	OR (95% CI)	P value
Patient N	575	25597		
Mean age (y±SD)	56 ± 17	66 ± 17	--	<0.001
Age > 75y	80 (14%)	9827 (38%)	0.26 (0.21-0.33)	<0.001
BMI	28.4 ± 5.1	27.7 ± 5.2	--	0.004
Previous VTE	115 (20%)	3960 (16%)	1.4 (1.1-1.7)	0.003
Cancer	59 (10%)	5448 (21%)	0.4 (0.3-0.6)	<0.001
Immobilization due to neurologic disease	0 (0%)	922 (3.6%)	--	<0.001

Characteristics of Patients with a Recent Travel History and Other Patients in the Registry [2]

	Recent travelers	Other patients in registry	OR (95%CI)	P value
Recent surgery	20 (3.5%)	3235 (13%)	0.3 (0.2-0.4)	<0.001
Hormone use	49 (8.7%)	943 (3.7%)	2.5 (1.8-3.3)	<0.001
Pregnancy	4 (3.5%)	168 (4.7%)	0.7 (0.3-2.0)	NS
Positive thrombophilia test	92 (16%)	2187 (8.7%)	2.0 (1.6-2.6)	<0.001
CHF	11 (1.9%)	1440 (5.9%)	0.3 (0.2-0.6)	<0.001
Chronic lung disease	38 (6.6%)	2544 (9.9%)	0.6 (0.5-0.9)	<0.001
Other underlying disease	21 (3.7%)	12229 (48%)	0.7 (0.6-0.8)	<0.001
Abnormal creatinin level	41 (7.2%)	3770 (15%)	0.4 (0.3-0.6)	<0.001
Use of LMWH prophylaxis	14 (2.4%)	3377 (13%)	0.2 (0.1-0.3)	<0.001

Tzoran Thromb Res, 2010

Risk Strafication

- Risk stratification model can be suggested for efficient thromboprophilaxis to patients at risk during long-haul traveling.
- Young healthy patients with previous VTE, high BMI, hormone use, and known thrombophilia are at high risk for travel-related thrombosis.

Tzoran Thromb Res, 2010

Mechanisms - WRIGHT I

- 71 Volunteers exposed to 8 hour flight and 8 hour immobilization in a cinema compared to normal daily activity .
- Evidence for clotting activation during and after flying in 16% volunteers particularly in women who used contraceptives and had FVL

Schreijer Lancet, 2006

Coagulation Factors and Travel-Related VTE

334 travelers (200 patients 134 controls)

- High factor II 2.2 (1.3-3.7)
- High factor VIII 6.2 (3.6-10.5)
- High factor IX 3.2 (0.9-11.0)
- High fibrinogen 2.0 (0.7-5.5)
- OC + high FVIII 52 (5.4-498)

Kuipers Blood, 2009

Mechanisms for Clotting on Air

- Increase in factor VIII
- Increase in PAI-1
- Increase in sP-selectin
- Basic Mechanism - Hypoxia

Schreijer JTH, 2010

Effects of Hypoxia – Experimental Evidence

- Increased procoagulant activity
- Inhibition of fibrinolysis
- Upregulation of the transcription factor early-response-growth gene product (Egr-1) upregulates tissue factor transcription

Gertler J Vasc Surg, 1991
Gertler J Vasc Surg, 1993
Yan PNAS, 1998

Hypoxia and Thrombosis

- Hypoxia triggers VTE in COPD, neonates, sleep apnea , high altitude, air-travel and in experimentally-induced hypoxia.
- Hypoxia is associated with thrombocytosis and increased platelet activation.
- Role for microparticles?

Can we Identify Those at Risk?

- 58 consecutive VTE patients within 1 month of travel.
- One risk factor 84%
- Two risk factors 52%
- Hormonal therapy 24%
- Factor V Leiden 24%
- Previous VTE 24%

McQuillan, Blood Coag Fibrinol 2003

Travel and Thrombophilia

TRAVEL	THROMBOPHILIA	OR
NO	NO	1
NO	YES	6.6(3.9-11.3)
YES	NO	1.7(0.7-4)
YES	YES	16.8(3.8-75)

Martinelli Arch Intern Med, 2003

Travel and Hormonal Therapy

TRAVEL	OC	OR
NO	NO	1
NO	YES	4.2(1.9-9.3)
YES	NO	1.8(0.4-7.6)
YES	YES	23.4(2.6-211)

Martinelli Arch Intern Med,2003

Air Travel and Gestational VTE

- Women with thrombophilia are at increased risk of VTE during pregnancy.
  - 1/300 for factor V Leiden or factor II G20210A heterozygotes
  - 1/50 for factor V Leiden homozygotes or those with combined factor V Leiden and factor II mutations
- Following a long-haul flight the risk for VTE increases exponentially with flight duration (4 folds over 8 hours, 8 folds over 12 hours).

Air Travel and Gestational VTE

- Standard risk thrombophilia (FVL and PTM heterozygotes) may confer significant thrombotic risk in pregnancy following a long-haul flight.
- A pregnant woman with combined or severe thrombophilia is at a great risk of symptomatic VTE.
- This level of risk brings about issues of VTE prophylaxis in pregnant passengers.

Pregnant Women Perspective

- Consecutive pregnant women at 3rd trimester were given a questionnaire regarding air travel.
- 138/151 replied , over 50% had traveled during pregnancy.
- Only a third asked for a prior advice (GP, Midwife).
- A quarter did not know about travel related thrombosis.
- Over a third traveled without sufficient insurance.

Kingman J Travel Med, 2003

Thromboembolism and Air Travel – Obstetricians Advice Survey

- RCOG questionnaire

  1349 Ob Gyn - 690 (51%) available for analysis

- Suggested Prophylaxis:

  Mobilization – nearly all

  Aspirin – 53%

  GES – 49%

  LMWH – 4%

Voss J Obsted Gynecol, 2004

Air Travel and Pregnancy Complications Theoretical Assumptions

- Hypoxic conditions during a long-haul flight can be deleterious for mother and fetus.
- Placental vascular hypoperfusion can be found in women with IUGR, preeclampsia and placental abruption.
- Prolonged hypoxic conditions can induce reduced placental oxygenation and potentially throphoblasts injury .
- This may be particularly relevant for older pregnant women (over 35 years), and those with complicated pregnancies (twin gestation, hypertension, IUGR or diabetic pregnancies).

Air Travel and Pregnancy Complications

- Women with thrombophilia, especially those with antiphospholipid syndrome but also heritable thrombophilia, are at increased risk of pregnancy complications.
- Surprisingly, virtually no studies have looked at these issues, despite the fact that a large number of pregnant women do travel yearly on long-haul flights.

Air Travel and Pregnancy Complications

Retrospective analysis in 992 women.

	Travelers	Controls
	546	447
Primigravida	57%	54%
Delivery (w)	36±0.8	39±2.0
Birth weight (g)	2684±481	3481±703

Chibber Aust NZ J Ob Gyn, 2006

By Aukrust - Courtesy of Bjørn Bendz

Posture, Hydration and Coagulation Activation

- Dehydration increases thrombotic risk.
- Fluid loss does not explain coagulation activation in air travelers. Schreijer Thromb Haemost, 2008
- Upright position increases coagulation activation Masoud Hypertension, 2008
- Hydration do not alleviate increased coagulation in this setting Massoud, Thromb Haemost, 2010

Behavioral Risk Factors

80 patients 108 controls

	OR	95%CI
Window sitting	2.2	(1.1-4.4)
Anxiety	2.5	(0.9-7.0)
Sleeping	1.5	(0.7-3.1)
Alcohol	1.1	(0.5-2.4)

Schreijer BJH, 2009

The Elastic Stockings Study

- Aim- to determine frequency of DVT during long-haul economy class travel and evaluate efficacy of elastic stockings in DVT prevention.
- Subjects- 231 air travelers more than 50 years without prior thromboembolism.
- Evaluation- Duplex sonography before and after flight

scurr Lancet, 2001

Patient Characteristics

	No stockings	Stockings
Number	116	115
Age (years)	62 (56- 68)	61 (56-66)
Flying time (hours)	22 (18-36)	24 (19-35)
Thrombophilia	8	7

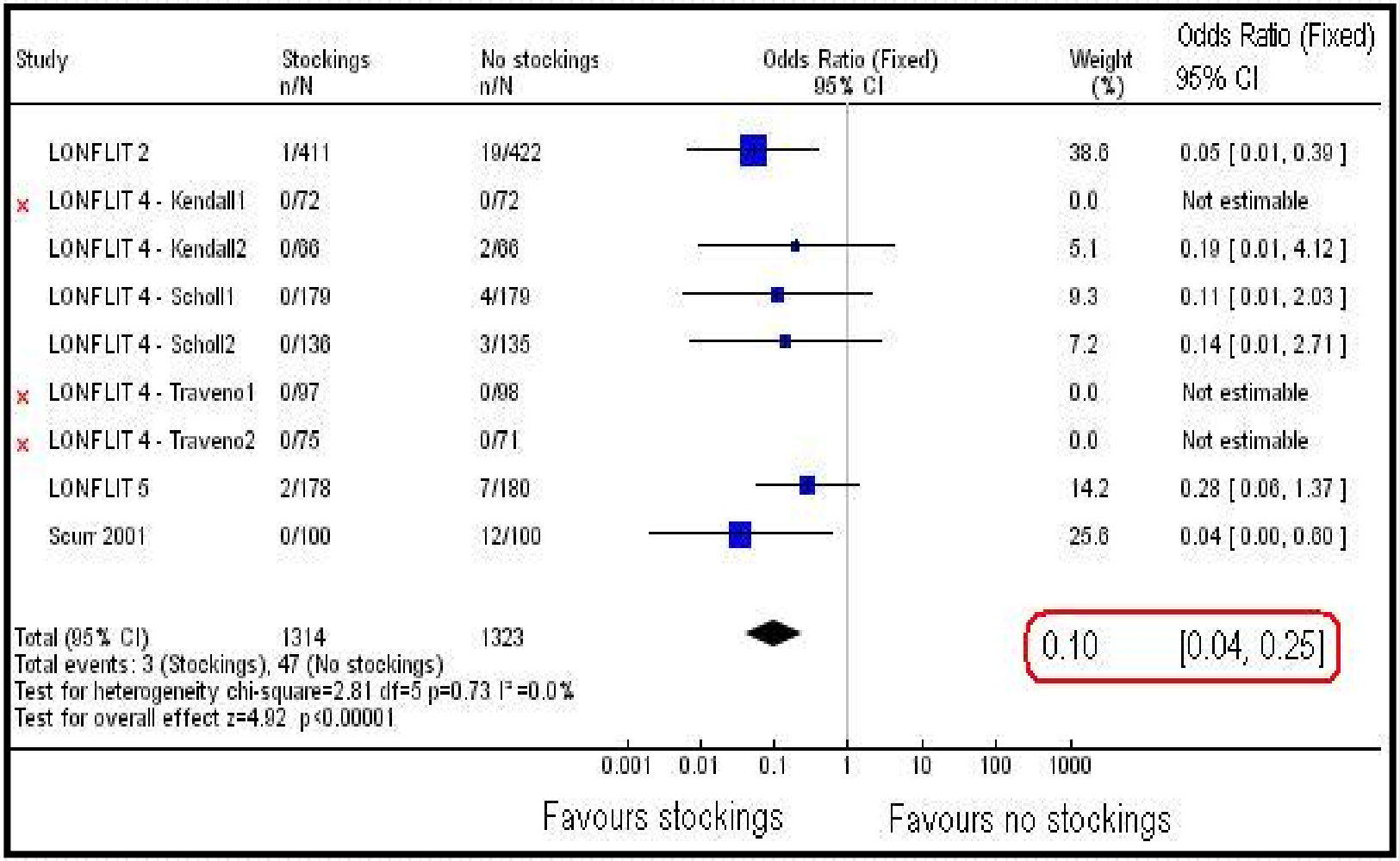
Scurr Lancet, 2001

Results

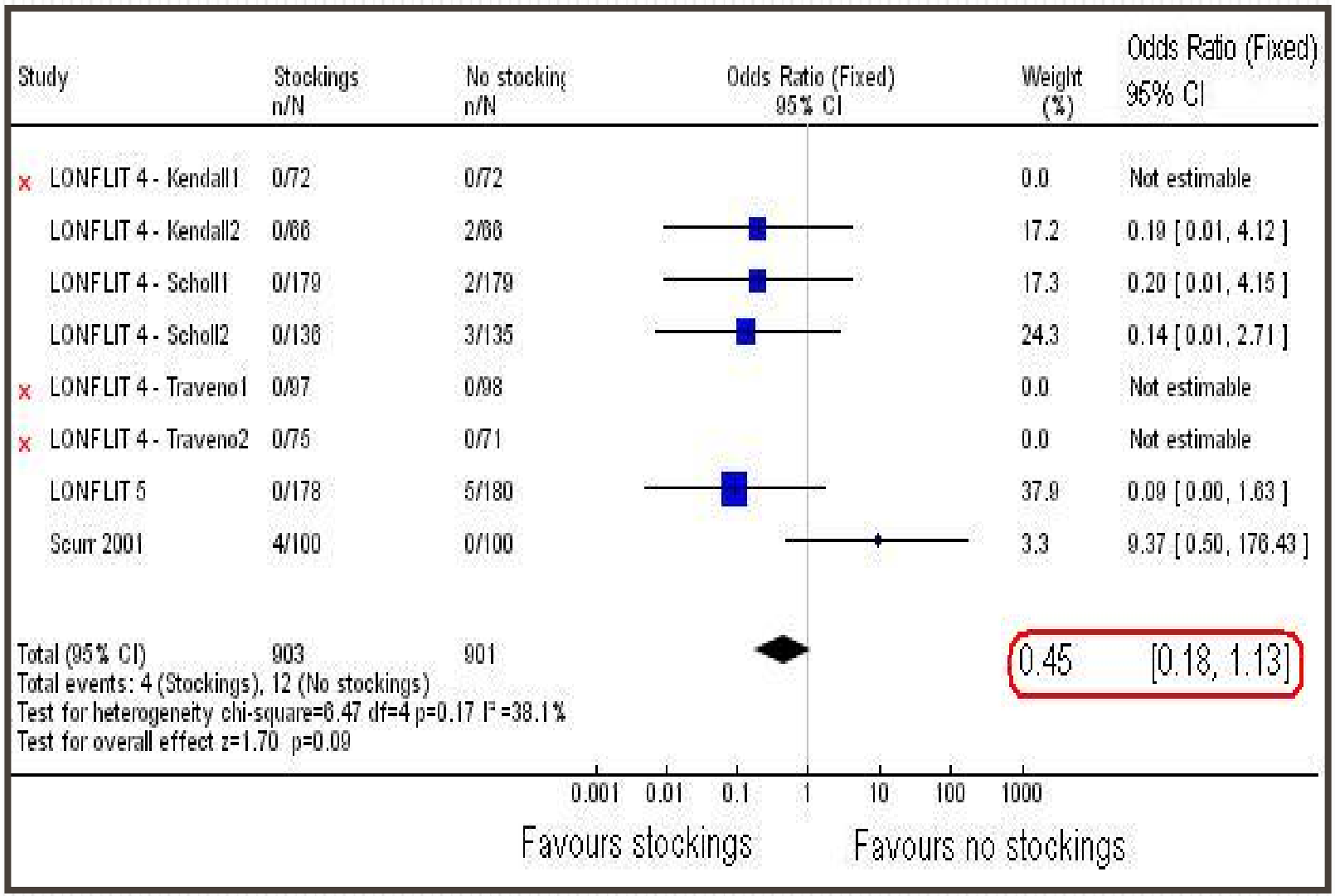
	No stockings	Stockings
Number	100	100
Symptomatic DVT	0	0
Asymptomatic DVT	12	0
Superficial Thrombophlebitis	0	4

Scurr Lancet, 2001

Ultrasound Detected Asymptomatic Deep Venous Thrombosis



Superficial Vein Thrombosis



Stockings for VTE Prevention Cochrane Review

- Source – Cochrane PVD Register, Central, Medline, Embase
- Selection – Randomized trials.
- 9 trials (n=2821).
- 7-low to medium risk (n=1548)
- 2-high risk (n=1273)
- All flights ≥ 7 hours
- Follow- up (US) available on 2637 participants
- Symptom less DVT – 50
- No stockings – 47 stocking 3
- OR – 0.1 95% CI 0.04-0.25, P<0.00001

Mechanical Devices

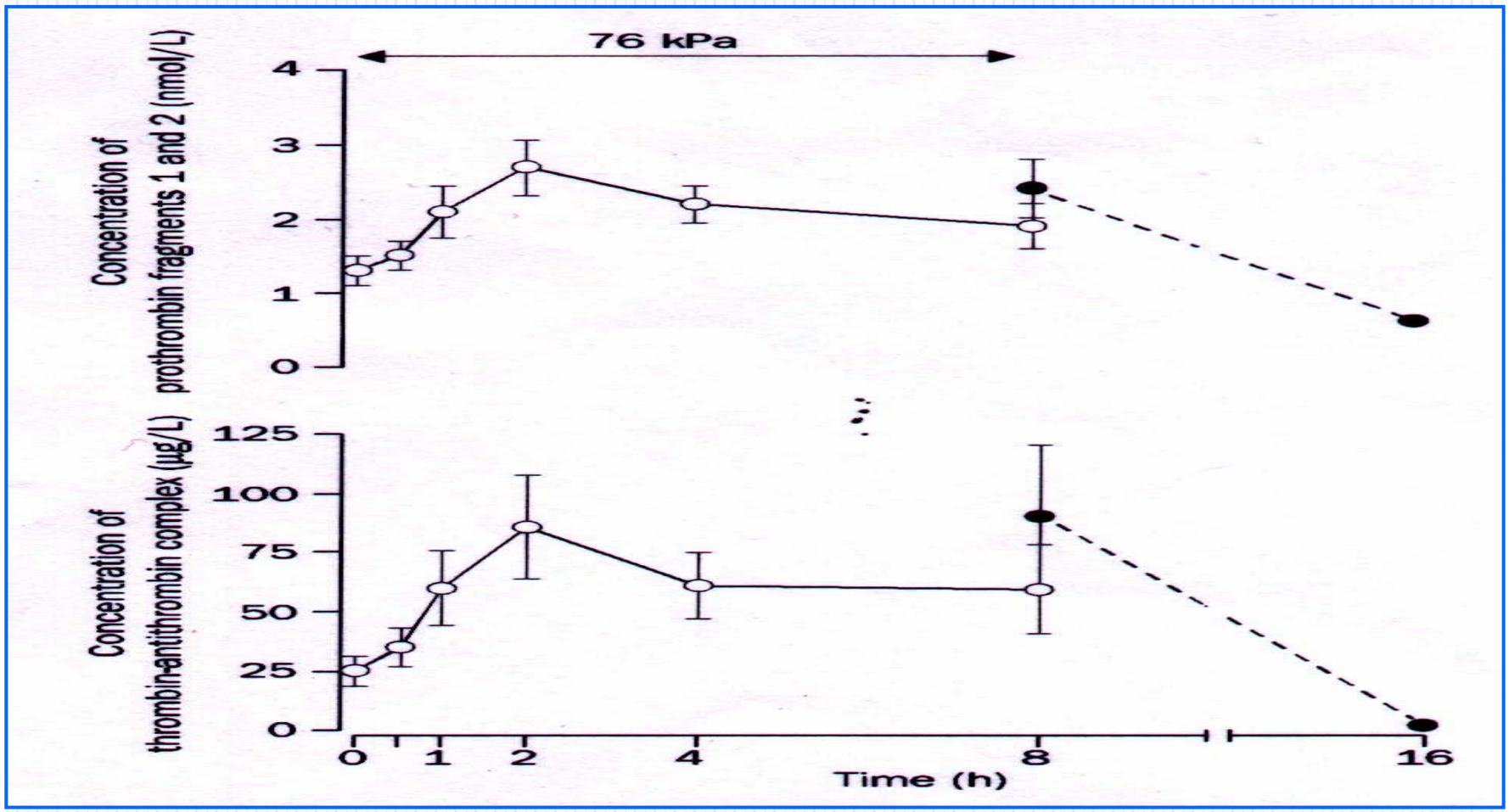
- 3 calf pump facilitating devices (PFD)
- 2 battery operated IPC
- 17 healthy volunteers on ground, 8 of them also on flight.
- Hemodynamic effects:

  - No difference between PFD and active foot movement

  - IPC significantly less active than PFD

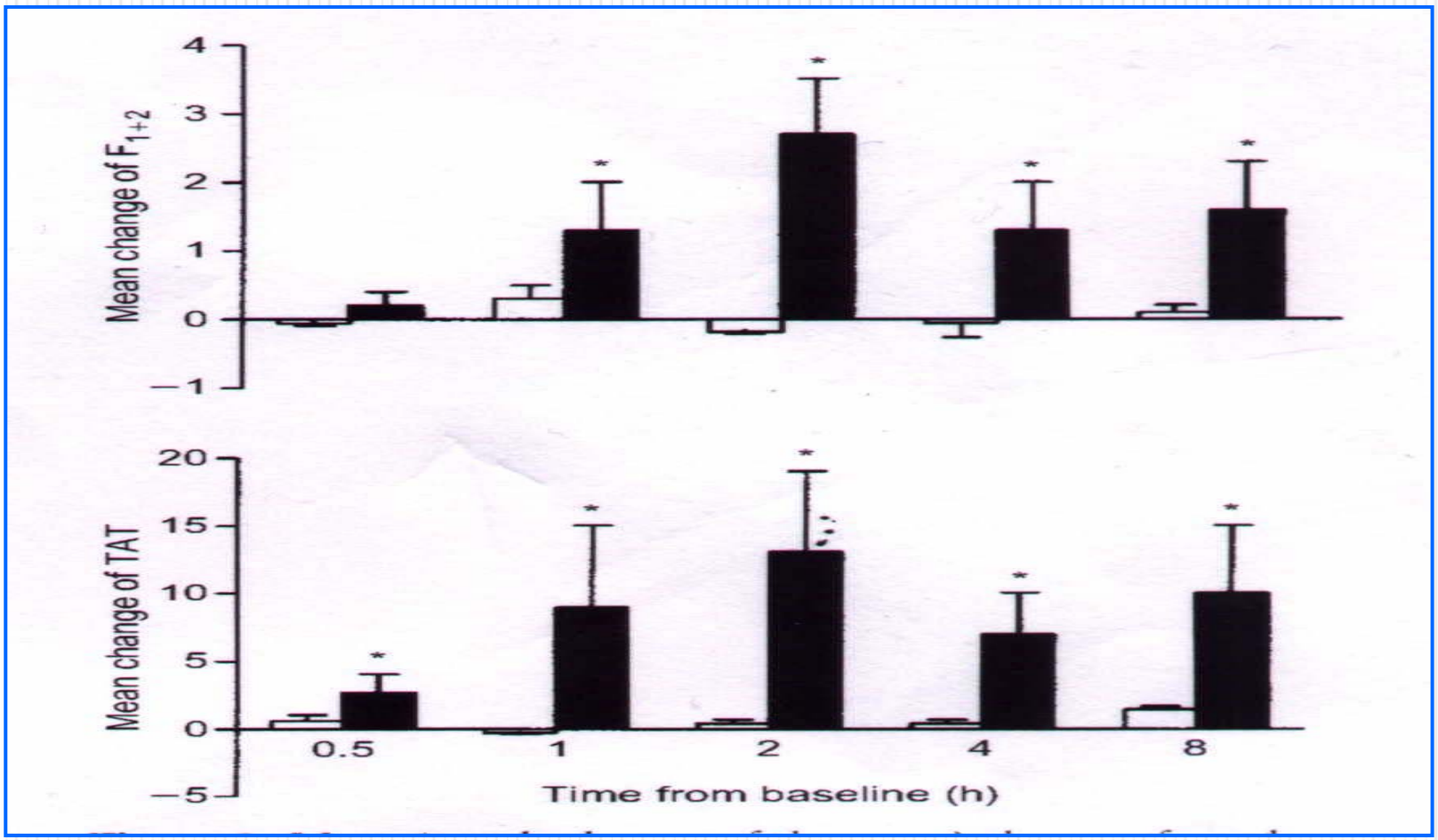
Lurie J Vasc Surg, 2006

Coagulation Activation in Hypobaric Chamber



Bendz Lancet, 2001

Enoxaparin Effect on Coagulation



Bendz Blood Coag Fibrinol, 2001

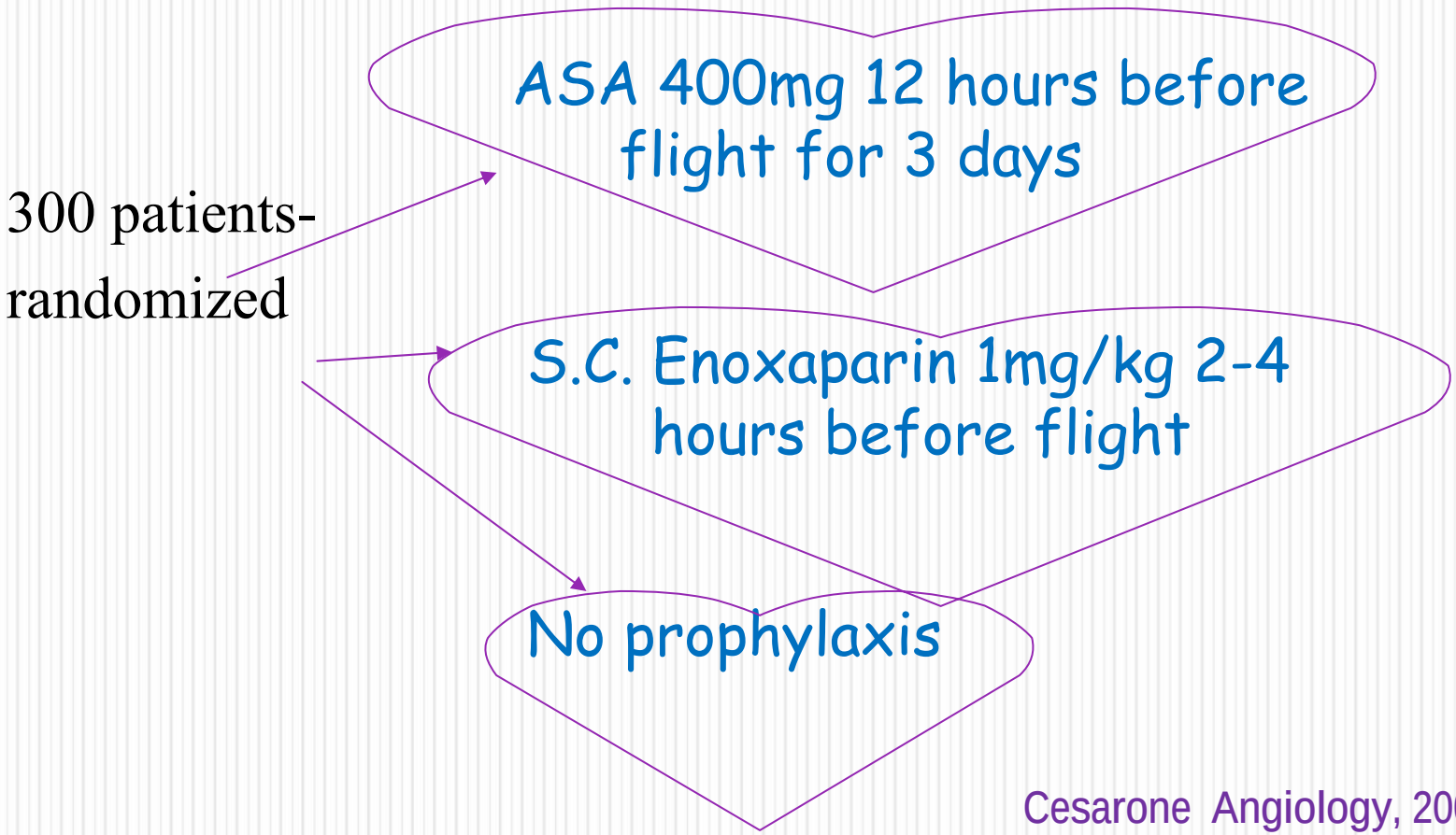
LONFLIT III study

- Aim- to evaluate the efficacy of enoxaparin or aspirin to prevent DVT among long haul travelers.
- Subjects- 300 passengers with previous heart disease or stroke.
- Flight duration >10 hours.

Cesarone Angiology ,2002

LONFLIT III - design

- Prospective randomized study



Cesarone Angiology, 2000

LONFLIT III- Results

- 52/300 failed to complete study (equally distributed)

	Enoxaparin	Aspirin	Control
Number	82	84	82
DVT	0	3 (3.6%)	4 (4.8%) P<0.002)
SVT	1	2	2

Cesarone Angiology, 2002

The Professionals Questionnaire

- ISTH, Cochrane, ISDB Congresses, Australia 2005
- Complete Q 2089 (53%)
- 80% used preventive measures
- Risk factors (90%) No risk factors (77%)
- LMWH (10% ISTH Vs 1% others)
- Drugs (31% MD Vs 11%-22% others)
- Dutch used the least (64%)
- Israeli used the most (94%)

Kuipers JTH, 2006

WRIGHT - II

- A randomized trial for prevention of travel-related thrombosis.
- 20-30,000 travelers
- 10,000 - regular measures
- 10,000 - mechanical prophylaxis
- 10,000 - antithrombotic prophylaxis ?

Medical Guidelines for Airline Travel

ASMA May 2003

Risk Categories (1)

Low

- Age over 40
- Obesity
- Active inflammation
- Recent minor surgery

Medical Guidelines for Airline Travel

ASMA May 2003

Risk Categories (2)

Moderate:

- Varicos veins
- Heart failure
- Recent myocardial infarction
- Hormonal therapy
- Polycythemia
- Pregnancy
- Lower limb paralysis
- Recent lower limb trauma

Medical Guidelines for Airline Travel

ASMA May 2003

Risk Categories (3)

High:

- Previous VTE
- Known thrombophilia
- Recent major surgery
- Previous CVA
- Malignancy
- Family history of VTE

Medical Guidelines for Airline Travel

ASMA May 2003

Prophylaxis

	Behavioral	Mechanical	Antithrombotic
Low	+	±	-
Moderate	+	+	-
High	+	+	+

Scoring System for Air Travel Related Thrombosis

- Age > 40 — 1
- Hormonal therapy — 2
- *Thrombophilia*
  - Moderate — 1
  - Severe — 3
- Active cancer — 2
- Recent surgery — 2
- Recent CVA — 1
- Varicose veins
- Previous VTE — 4

Scoring System for Air Travel Related Thrombosis

- Leg fracture 2
- Obesity 1
- CHF 1
- Pregnancy 2
- Flight duration
  - >8 hours 1
  - >12hours 2

Risk Stratification

- Low ≤ 4
- Moderate 5-8
- High > 8

Suggested Prophylaxis

- Low — Behavioral
- Moderate — Mechanical
- High — Anticoagulant

The Future is Here

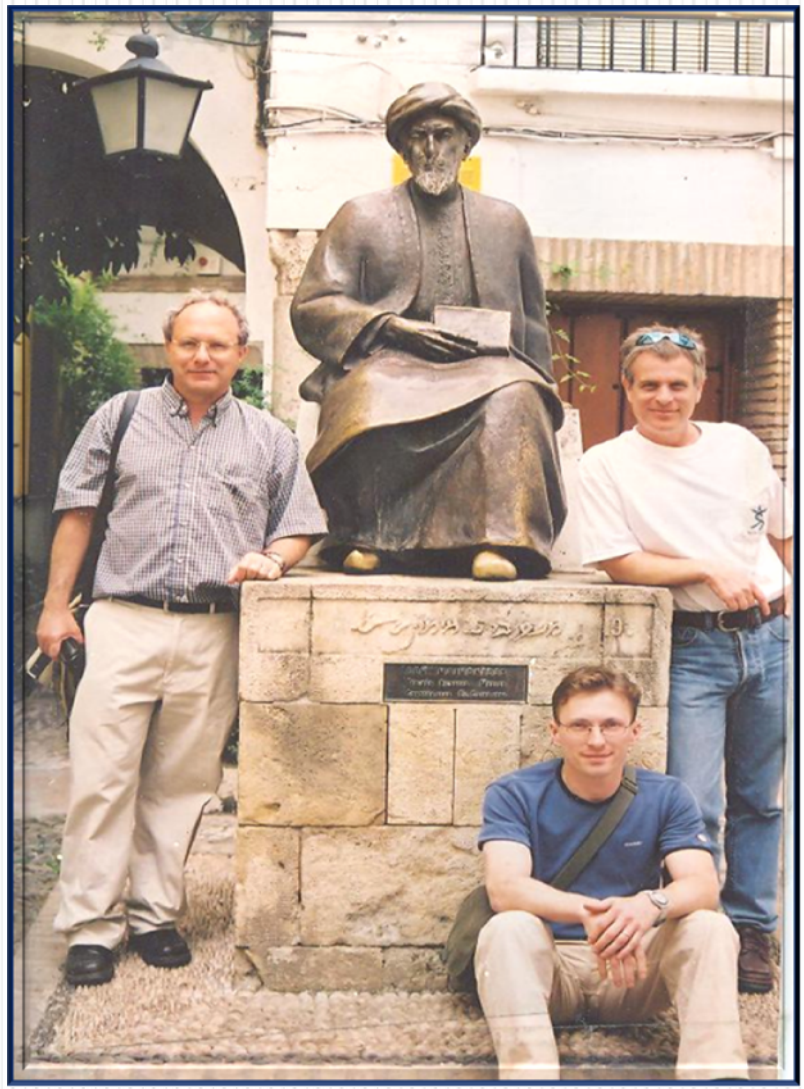
- Flights will be longer: “Boeing 777 is the most technologically advanced family of airplanes.
  The 777 seats up to 368 passengers with a range up to 17,446 km”
- Airbus 380 will carry over 700 passengers to the same distance
- Significantly higher risk for DVT, Jet lag, Infectious diseases transmission,prolonged hypoxia etc…

Traveler's Thrombosis: Airlines Still not Giving Passengers the WRIGHT Advice

- This study examined the impact of the world health organization's information given by airlines to their passengers regarding traveler's thrombosis.
- Only a quarter (27/107) of airlines warned of the risk of traveler's thrombosis.
- The majority of world airlines continue to fail to warn of the risk of traveler's thrombosis or to offer appropriate advice.

Scurr J Phlebology, 2010

CORDOBA



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