PARIS JOURNEES INTERNATIONALES ET FRANCOPHONES ANGEIOLOGIE 2015

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JIFA 2015

67e ANNIVERSAIRE DE LA SFA

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AGRÉÉ PAR LE CONSEIL RÉGIONAL DE FORMATION MÉDICALE CONTINUE - CFEE : N° 11753436775

Biomarqueurs du syndrome post-thrombotique et conséquences thérapeutiques

Prof. Stefano de Franciscis

UMG
Università Magna Græcia di Catanzaro
Dubium sapientiae initium

Scuola di Specializzazione in Chirurgia Vascolare
sede UMG
Coordinatore : Prof. Stefano de Franciscis

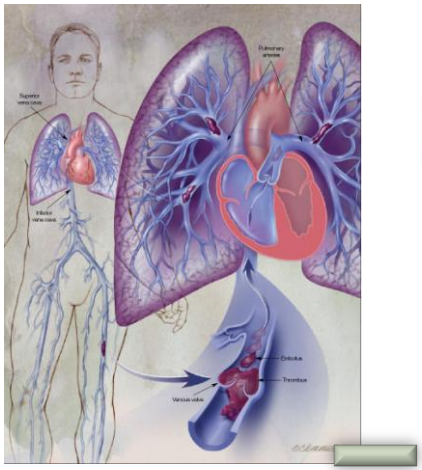
Presenter Disclosure Information

- FINANCIAL DISCLOSURE:
  No relevant financial relationship exists

- CONFLICT OF INTEREST DISCLOSURE:
  The presenter declares that he has no competing interests

Venous Thromboembolism (VTE)

- includes deep vein thrombosis (DVT) and pulmonary embolism (PE)
- is the third most common cardiovascular disorder
- Incidence: 0.1% ; prevalence: 2- 5%
- Approximately 20% of patients with PE will die before diagnosis or on the first day
- Approximately 20–50% of patients develop PTS.



MANAGEMENT OF THROMBOEMBOLIC DISEASE

The diagnosis and treatment of venous thromboembolism

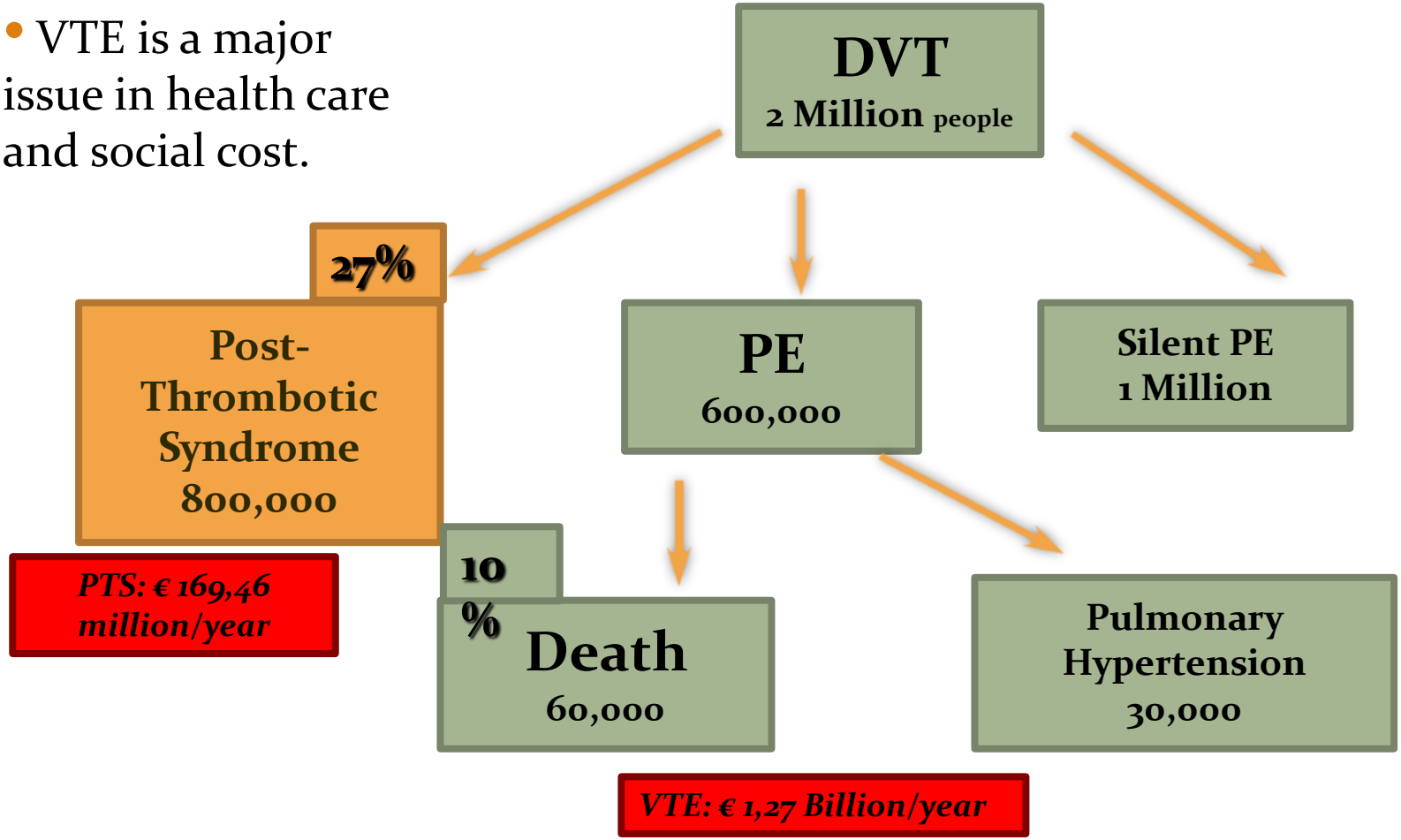
Philip Wells[1] *and David Anderson*[2]

[1]*Department of Medicine, University of Ottawa and the Ottawa Hospital, Ottawa Hospital Research Institute, Ottawa, ON; and* [2]*Department of Medicine, Dalhousie University and Capital Health, Halifax, NS*

Hematology 2013

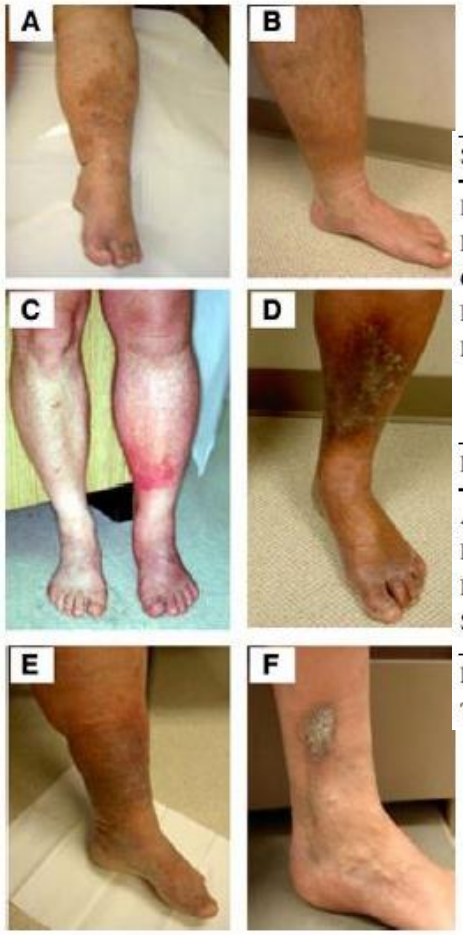
Economic burden of VTE (Western Countries)

- VTE is a major issue in health care and social cost.



Goldhaber SZ et al Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER) Lancet 1999;353:1386-1389.

The Post-Thrombotic Syndrome



- After DVT 20–50% of patients develop PTS.

Villalta score for PTS

Subjective symptoms	Objective signs
Heaviness	Pretibial edema
Pain	Induration of the skin
Cramp	Hyperpigmentation
Pruritus	New venous ectasia
Paresthesia	Redness
	Pain during calf compression
	Ulceration of the skin

PTS	Score
Absent	≤4
Mild	5–9
Moderate	10–14
Severe	≥15 or a venous ulcer is present

Each sign or symptom is graded with a score between 0 and 3
The presence of ulceration is only noted

- The Villalta score has recently been adopted as the reference clinical classification of PTS: it grades the severity of five patient-rated symptoms and six clinicianrated clinical signs, ranging from 0 (absent) to 3 (severe).

AHA Scientific Statement

The Postthrombotic Syndrome: Evidence-Based Prevention, Diagnosis, and Treatment Strategies
A Scientific Statement From the American Heart Association

Susan R. Kahn, MD, MSc, FRCPC, Chair; Anthony J. Comerota, MD; Mary Cushman, MD, MSc, FAHA; Natalie S. Evans, MD, MS; Jeffrey S. Ginsberg, MD, FRCPC; Neil A. Goldenberg, MD, PhD; Deepak K. Gupta, MD; Paolo Prandoni, MD, PhD; Suresh Vedantham, MD; M. Eileen Walsh, PhD, APN, RN-BC, FAHA; Jeffrey I. Weitz MD, FAHA; on behalf of the American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing

Circulation. 2014;130:1636-1661

CEAP classification for PTS

Clinical signs	
Class 0	No visible or palpable signs of venous disease
Class 1	Telangectasia or reticular veins
Class 2	Varicose veins
Class 3	Edema
Class 4	Skin changes ascribed to venous disease
Class 5	Skin changes as described above with healed ulceration
Class 6	Leg ulceration, skin changes as defined above
Etiological classification	Congenital, primary, secondary
Anatomical distribution	Superficial, deep, or perforating, alone or in combination
Pathophysiological dysfunction	Reflux or obstruction, alone or in combination

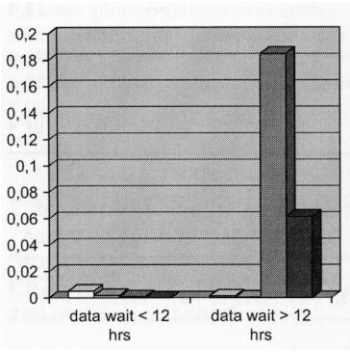
Post-thrombotic syndrome : the forgotten complication of venous thromboembolism

- ...So far, treatment options are limited and strategies that prevent PTS occurrence are therefore of major importance...

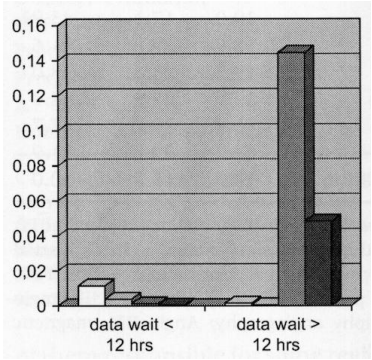
Guidelines for venous thromboembolism and clinical practice in Italy: a nationwide survey. (de Franciscis S et al. Ann Vasc Surg. 2008;22(3):319-27.)

146 centers (20.4% of total and 68.2% of the sample): 48 departments of general surgery, 46 departments of gynecology, and 52 departments of orthopedics.

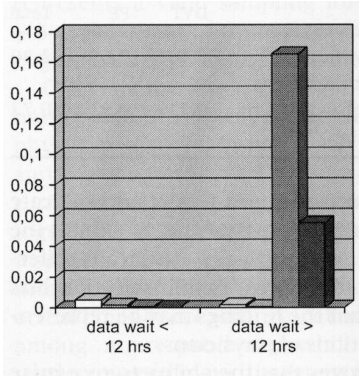
Diagnostic data waiting is related to mortality



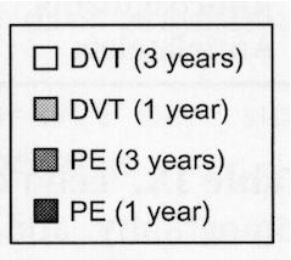
EcocolorDoppler



Angio-TC



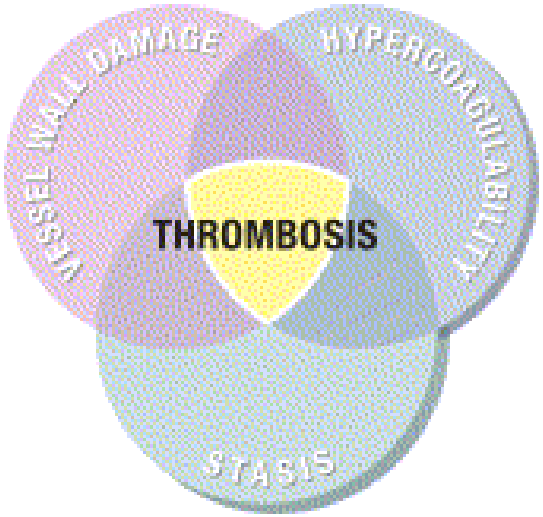
D-Dimer



• *Indications about DVT/PE prophylaxis (knowledge of the risk factors):* About 70% of the centers possessed some appropriate information.
•The diagnostic procedures to consider in case of suspected DVT are correctly followed by about 80% of the centers, while in case of suspected PE (similar to the choice between angio-TC and Perf-Scint) the percentage rises to 90%.
• *Annual and triennial mortality for DVT/PE (number of cases per 100,000 inhabitants):* total mortality for DVT is probably due to PE events not diagnosed in patients with DVT.
• *Prophylaxis:* About 90% of the centers employ LMWH or OA for prophylaxis; physical devices are used in 40% of cases.

Virchow triad

1856



Rudolf Virchow – 1821-1902.

Pergamon

Thrombosis Research 101 (2001) 321–327

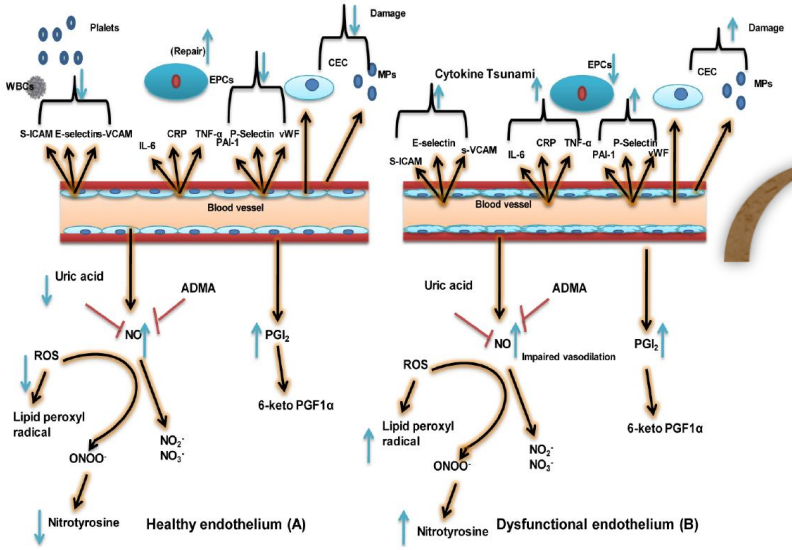
THROMBOSIS RESEARCH

Virchow's Triad Revisited: The Importance of Soluble Coagulation Factors, the Endothelium, and Platelets

Andrew D. Blann and Gregory Y.H. Lip
Haemostasis, Thrombosis, and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham B18 7QH, UK

The Vascular Endothelium and Human Diseases

- The endothelium plays a crucial role in providing the proper haemostatic balance.
- The function of endothelial cells far exceeds that of providing a non-thrombogenic inner layer of the vascular wall that helps to maintain blood fluidity.



Blood Reviews
Volume 2, Issue 2, June 1988, Pages 88–94
ELSEVIER

Vascular endothelium, haemostasis and thrombosis

C.N. Chesterman

IVYSPRING INTERNATIONAL PUBLISHER
International Journal of Biological Sciences
2013; 9(10):1057-1069. doi: 10.7150/ijbs.7502

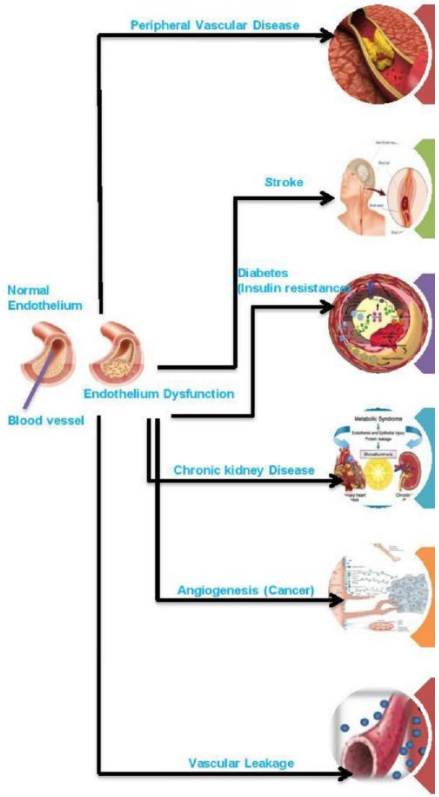
Review

The Vascular Endothelium and Human Diseases

Peramaiyan Rajendran[1], Thamaraiselvan Rengarajan[1], Jayakumar Thangavel[2], Yutaka Nishigaki[1], Dhanapal Sakthisekaran[3], Gautam Sethi[4], and Ikuo Nishigaki[1]✉

Endothelial Dysfunction

Endothelial dysfunction has been reported to be the initial step in the main vascular disease and represents overall functional changes characterized by vasospasm, coagulation abnormalities, and increased vascular proliferation.



- Arterial and venous thrombosis have always been regarded as different pathologies

BUT

- A common denominator might be represented by endothelial dysfunction.

AGE (2012) 34:751–760
DOI 10.1007/s11357-011-9265-x

Idiopathic deep venous thrombosis and arterial endothelial dysfunction in the elderly

Gianluigi Mazzoccoli · Andrea Fontana · Massimo Grilli · Mariangela Pia Dagostino · Massimiliano Copetti · Fabio Pellegrini · Gianluigi Vendemiale

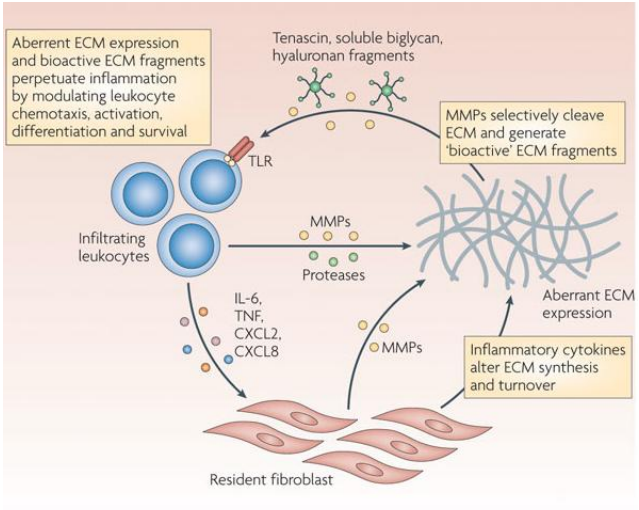
Endothelial Dysfunction, Inflammation and Vascular Disease

792 Biomed Environ Sci, 2013; 26(10): 792-800
Original Article

Relationship of Inflammation and Endothelial Dysfunction with Risks to Cardiovascular Disease among People in Inner Mongolia of China*

PENG Hao[1,§], HAN Shu Hai[2,§], LIU Hai Ying[2], Vasisht CHANDNI[4], CAI Xiao Qing[3], and ZHANG Yong Hong[1,#]

- It was demonstrated that Cardiovascular Disease risk factors were associated with **inflammation** and endothelial dysfunction
- Most of evidences were conducted in populations in Western countries and failed to take all the known confounders such as alcohol consumption, obesity, and hyperglycemia into consideration
- Several proinflammatory cytokines and growth factors, as IL-1a and b , IL-2, IL-17, IGF-1, TGF-a, and TNF-a, modulate the activity of **MMPs** supporting inflammatory process and mediate tissue injury

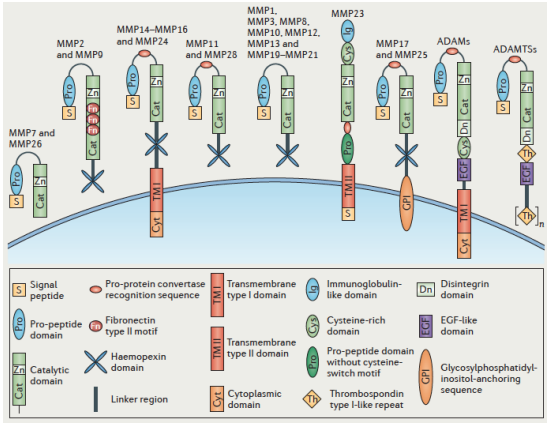


Metalloproteinases and their natural inhibitors in inflammation and immunity

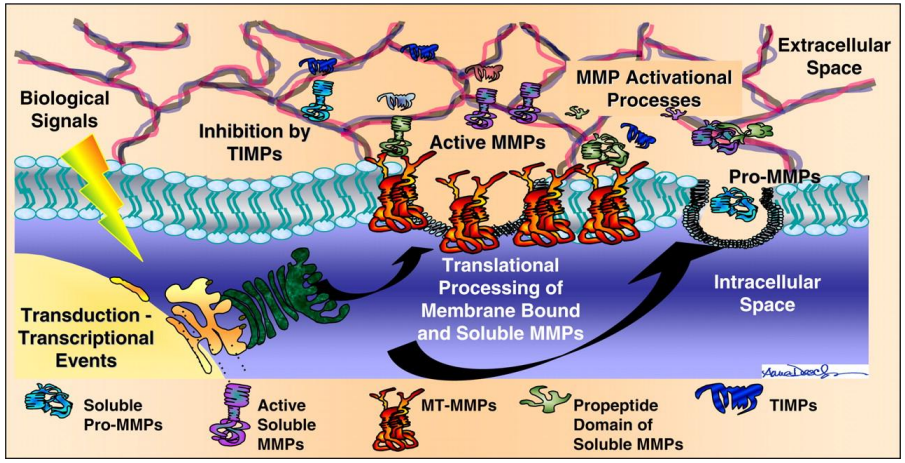
Rama Khokha, Aditya Murthy and Ashley Weiss**

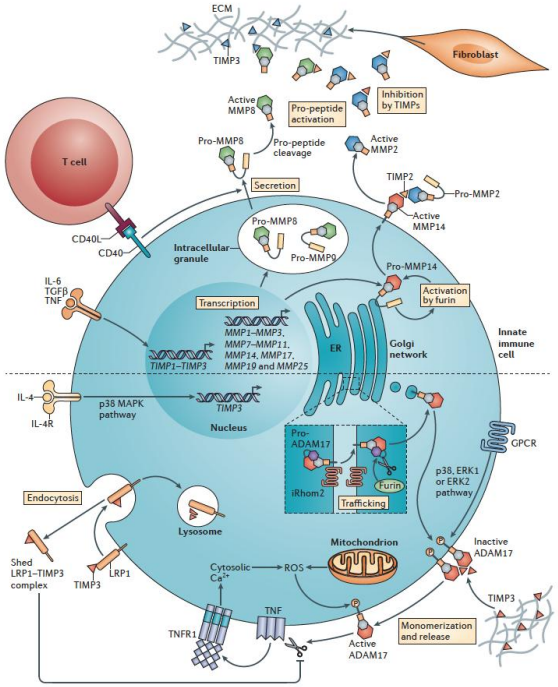
NATURE REVIEWS | IMMUNOLOGY 2013;13(9):649-65.

MMPs: Biology and Physiology



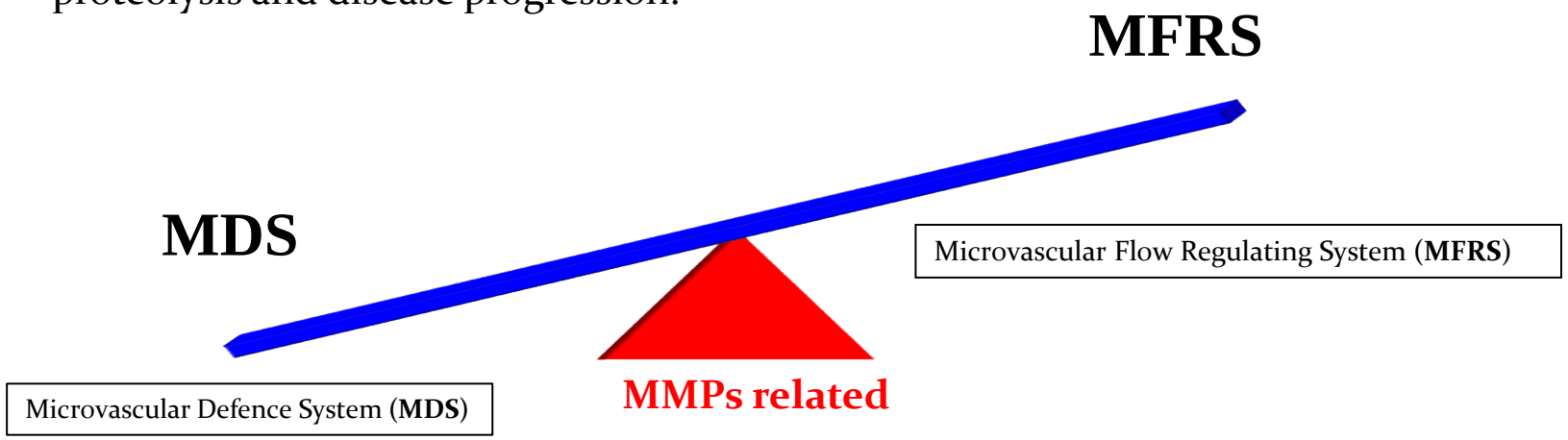
- There are 24 MMP genes in humans, including a gene duplication, and these genes encode 23 unique MMP proteins.





MMPs: Biology and Pathology

- Metalloproteinase regulation becomes aberrant in immune cells in many vascular inflammatory diseases: local factors contribute to altering the balance between metalloproteinases and their inhibitors to favour excess proteolysis and disease progression.



international wound journal
International Wound Journal ISSN 1742-4801

ORIGINAL ARTICLE

Biomarkers in post-reperfusion syndrome after acute lower limb ischaemia

Stefano de Franciscis[1,2], Giovanni De Caridi[3], Mafalda Massara[3], Francesco Spinelli[3], Luca Gallelli[4], Gianluca Buffone[1], Francesco G Caliò[5], Lucia Butrico[2], Raffaele Grande[2] & Raffaele Serra[1,2]

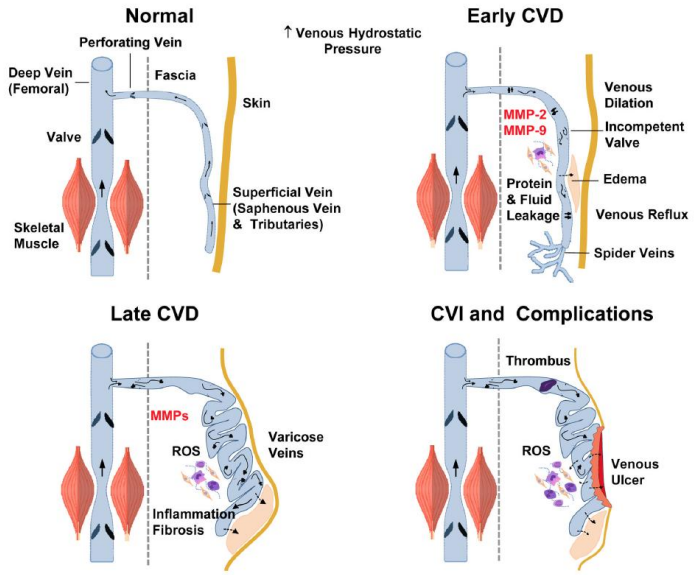
Vascular

The role of matrix metalloproteinases and neutrophil gelatinase-associated lipocalin in central and peripheral arterial aneurysms

Raffaele Serra, MD, PhD,[a,b] Raffaele Grande, MD,[a] Rossella Montemurro, MD,[a] Lucia Butrico, MD,[a] Francesco Giuseppe Caliò, MD,[c] Diego Mastrangelo, MD,[d] Edoardo Scarcello, MD, PhD,[e] Luca Gallelli, MD, PhD,[f] Gianluca Buffone, MD,[a] *and* Stefano de Franciscis, MD,[a,b] *Catanzaro, Telese Terme, and Cosenza, Italy*

2015;157(1):155-62. SURGERY

Venous disease, inflammation and MMP



- Late stages of CVD are associated with further **increases in MMPs**, varicose veins, edema, vein tissue remodeling, inflammation and fibrosis. CVD is complicated by thrombophlebitis, further increases in ROS (Reacting Oxygen Species), and venous wound leg ulcer.

Published in final edited form as:
Curr Drug Targets. 2013 March 1; 14(3): 287–324.

Matrix Metalloproteinases as Potential Targets in the Venous Dilation Associated with Varicose Veins

Arda Kucukguven and **Raouf A. Khalil**

2013;21(3):395-401.
Wound Repair and Regeneration

Chronic venous leg ulcers are associated with high levels of metalloproteinases-9 and neutrophil gelatinase-associated lipocalin

Raffaele Serra, MD, PhD[1]; Gianluca Buffone, MD[1]; Daniela Falcone, PhD[2]; Vincenzo Molinari, MD[1]; Monica Scaramuzzino, MSc[2]; Luca Gallelli, MD, PhD[2]; Stefano de Franciscis, MD[1]

Post Thrombotic Syndrome as chronic evolution of Deep Vein Thrombosis – Role of MMPs

Vein wall fibrotic injury following deep vein thrombosis (DVT) is associated with elevated MMPs

- While the association between DVT and post-thrombotic changes is well recognized, the progression from acute thrombosis to chronic fibrosis is still unclear.

J Vasc Surg. 2011 January ; 53(1): 139–146. doi:10.1016/j.jvs.2010.07.043.

Post Thrombotic Vein Wall Remodeling

Kristopher B. Deatrick, MD, Megan Elfline, MS, Nichole Baker, RVT, Catherine E. Luke, LVT, Susan Blackburn, MS, Catherine Stabler, RN, Thomas W. Wakefield, MD, and Peter K. Henke, MD

The effect of matrix metalloproteinase 2 and matrix metalloproteinase 2/9 deletion in experimental post-thrombotic vein wall remodeling

Kristopher B. Deatrick, MD,[a] Catherine E. Luke, LVT,[a] Megan A. Elfline, BS,[a] Vikram Sood, BS,[a] Joseph Baldwin, BS,[a] Gilbert R. Upchurch, Jr, MD,[a] Farouc A. Jaffer, MD, PhD,[b] Thomas W. Wakefield, MD,[a] and Peter K. Henke, MD,[a] *Ann Arbor, Mich; and Boston, Mass*

JOURNAL OF VASCULAR SURGERY
November 2013

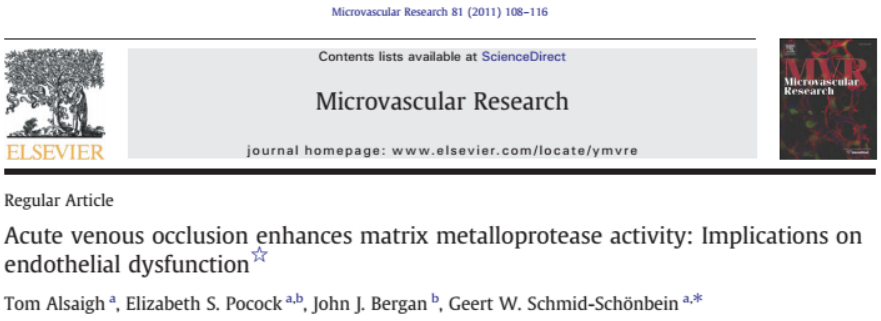
- Evidences have shown that MMPs is most significantly elevated in the vein wall after DVT at the middle and later timepoints.

The ability to predict severity of the post-thrombotic syndrome (PTS) *EARLY* after acute deep-vein thrombosis (DVT) is possible but yet unclear.

PTS Biomarker?

Deep Vein Thrombosis and MMPs in early stages

- Deep vein thrombosis (DVT) occurs when a blood clot (thrombus) forms in one or more of the deep veins in your body, usually in your legs. Deep vein thrombosis can cause leg pain or swelling, but may occur without any symptoms.


Microvascular Research 81 (2011) 108–116
Contents lists available at ScienceDirect
Microvascular Research
journal homepage: www.elsevier.com/locate/ymvre
ELSEVIER

Regular Article

Acute venous occlusion enhances matrix metalloprotease activity: Implications on endothelial dysfunction ☆

Tom Alsaigh [a], Elizabeth S. Pocock [a,b], John J. Bergan [b], Geert W. Schmid-Schönbein [a,*]

- A shift in hemodynamic stresses during venous occlusion serve as a stimulatory factor in the upregulation of degrading enzyme activity.
- The protease activation occurs within minutes and involves MMPs that are blocked by a broad range MMP inhibitor
- The presence of **MMPs** and TIMPs in acute venous occlusion model suggests that there is an important early **interplay** between protease and inhibitor during events that precede the development of venous disease.

Deep Vein Thrombosis and MMPs in late stages

- The process of recanalization leads to restoration of a flow channel even in cases of initial complete occlusion of the vein lumen by the acute thrombus

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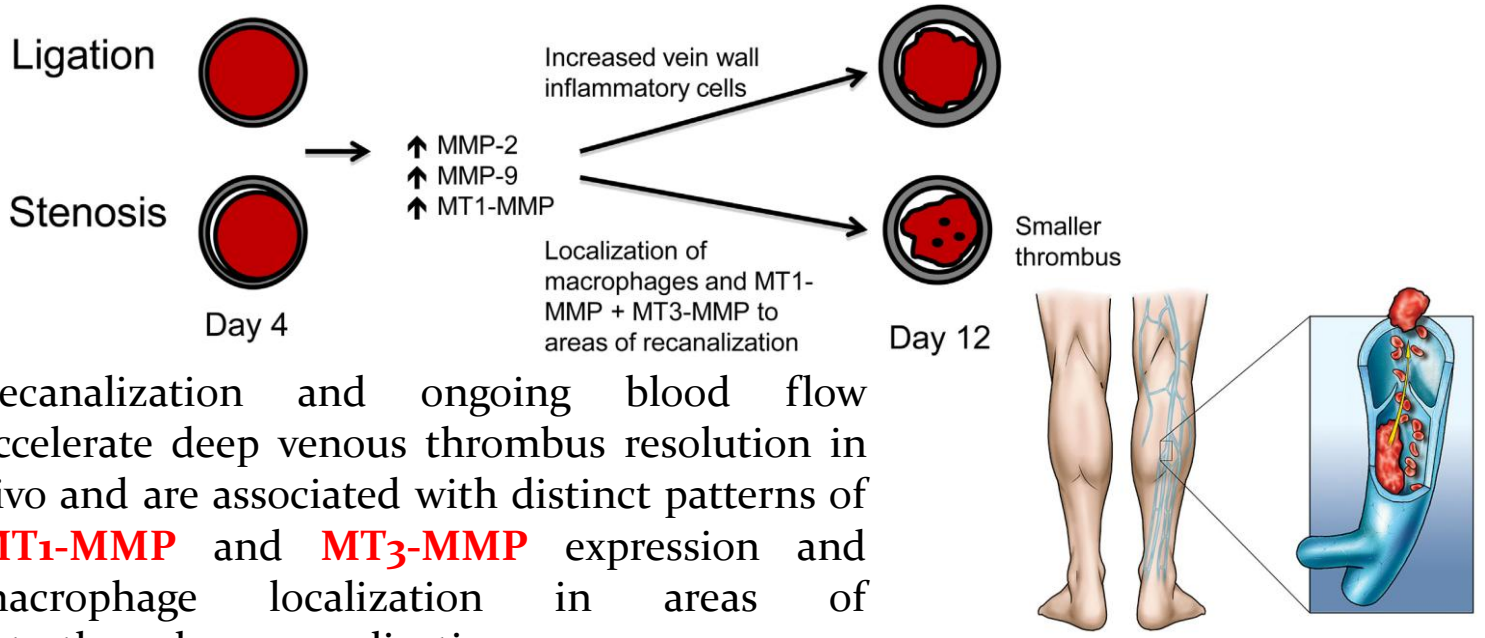
Journal of Vascular Surgery
Venous and Lymphatic Disorders™

BASIC RESEARCH STUDIES

From the Eastern Vascular Society

Recanalization and flow regulate venous thrombus resolution and matrix metalloproteinase expression in vivo

Christine Chabasse, PhD,[a,b] Suzanne A. Siefert, MD,[a,b] Mohammed Chaudry, MD,[a,b] Mark H. Hoofnagle, MD, PhD,[a,b] Brajesh K. Lal, MD,[b] and Rajabrata Sarkar, MD, PhD,[a,b] *Baltimore, Md*

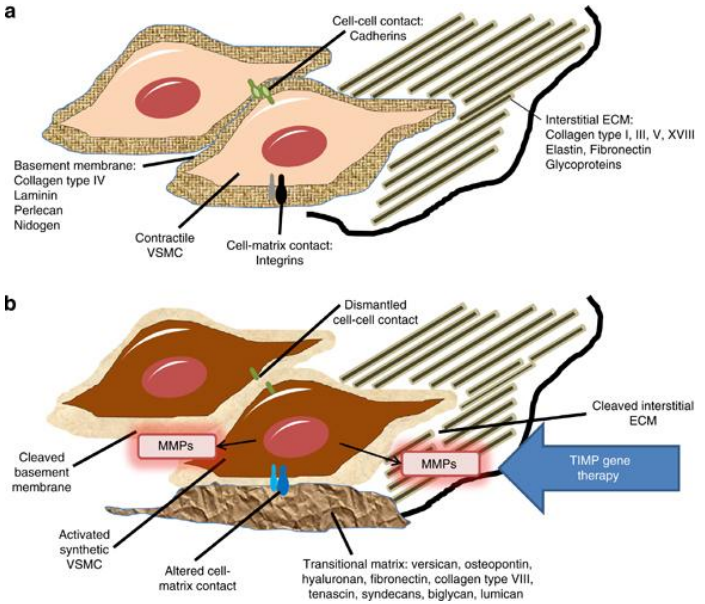


- Recanalization and ongoing blood flow accelerate deep venous thrombus resolution in vivo and are associated with distinct patterns of **MT1-MMP** and **MT3-MMP** expression and macrophage localization in areas of intrathrombus recanalization
- Macrophages → inflammation → fibrosis → SPT

MMPs, Stem Cells and PTS

VSMC: Vascular Smooth Muscle Cell
ECM: Extracellular Matrix

- Stem Cells are VSMCs progenitors
- VSMCs phenotype conversion, proliferation and migration play a significant role in the complex pathological process of venous pathophysiology.
- The process VSMCs migration from tunica media to the intima accompanied with ECM remodeling is a dynamic balance of matrix synthesis and degradation and MMPs play a pivotal role.



Zhu et al. Journal of Cardiothoracic Surgery 2013, 8:155
http://www.cardiothoracicsurgery.org/content/8/1/155
JCTS JOURNAL OF CARDIOTHORACIC SURGERY
RESEARCH ARTICLE Open Access

ECM-related gene expression profile in vascular smooth muscle cells from human saphenous vein and internal thoracic artery

Tian-xiang Zhu[1], Bin Lan[1*], Ling-ying Meng[2], Yan-long Yang[1], Rui-xiong Li[1], En-min Li[3], Shao-yi Zheng[4] and Li-yan Xu[3]

Stem cells, MMPs and tissues regeneration

- MMPs may regulate the behavior of VSMCs both in vitro and in vivo.
- MMPs permit the release of VSMCs from their surrounding basement membrane distrupting cell-cell contacts and promoting VSMC migration and proliferation into the intima and tissue regeneration.
- Non-specific **MMP inhibitors** or overexpression of **tissue inhibitors of MMPs** retard VSMC migration and the ensuing neointima formation.

ELSEVIER
Cardiovascular Research 69 (2006) 614 – 624
Cardiovascular Research
www.elsevier.com/locate/cardiores

Review

Matrix metalloproteinases regulate migration, proliferation, and death of vascular smooth muscle cells by degrading matrix and non-matrix substrates

Andrew C. Newby *

Matrix Metalloproteinase (MMP)-3 Activates MMP-9 Mediated Vascular Smooth Muscle Cell Migration and Neointima Formation in Mice

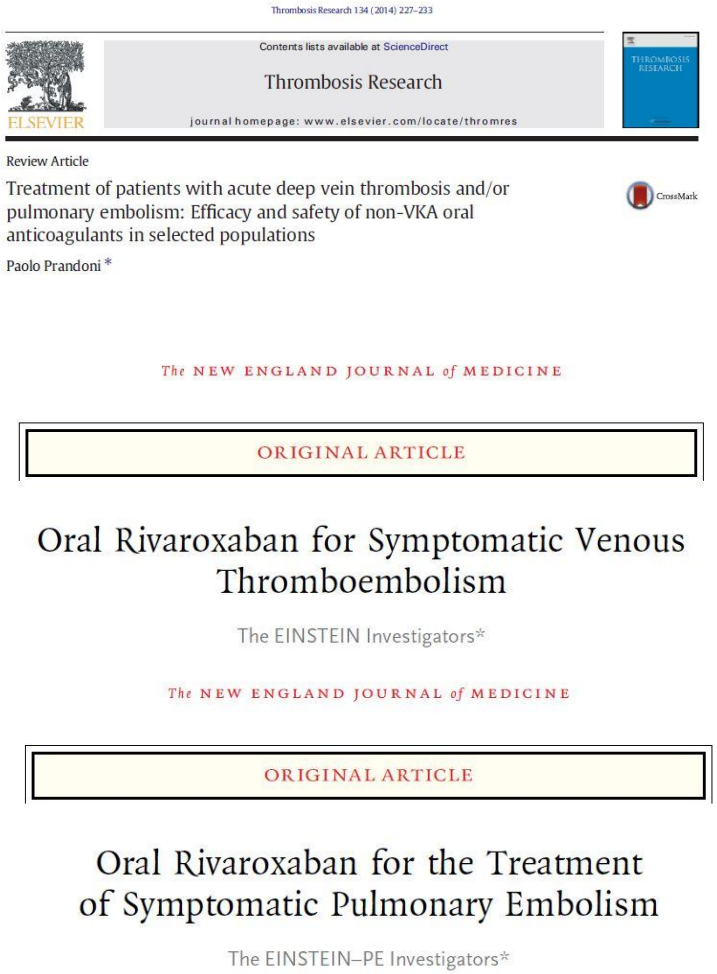
Jason L. Johnson, Amrita Dwivedi, Michelle Somerville, Sarah J. George, Andrew C. Newby

Arterioscler Thromb Vasc Biol **September 2011**

Current Recommendations for DVT and PE – Pharmacological Approach

- **LMWH** can be considered the initial choice for prophylaxis based on its efficacy, safety, cost effectiveness, and easy-to-administer once-daily dose regimens.
- **UFH** is a reasonable alternative agent and should be initially considered in patients with severe renal insufficiency.
- **Fondaparinux** should be the initial choice in patients with a history of HIT. Mechanical prophylaxis should be used in patients in whom pharmacologic prophylaxis is contraindicated, although these devices should be used with care.
- The **NVKA**, edoxaban and rivaroxaban have completed large phase III studies and demonstrated non-inferiority to standard therapy.

With the approval of rivaroxaban for the treatment and secondary prevention of DVT and PE, physicians now have an additional treatment option suitable for a wide range of patients with DVT and/or PE that also presents a favourable benefit–risk profile.



VTE– Biomolecular Pharmacology as prophylaxis

- **LMWH** can improve syntoms and signs of DVT through selective inhibition of main **MMPs**.

- **MMPs** play a pivotal role in pathophysiology of VTE and DVT.

ACTA PHLEBOL 2013;14:115-21

Pulmonary embolism, metalloproteinases and neutrophil gelatinase associated lipocalin

M. T. BUSCETI [1], R. GRANDE [1], B. AMATO [2, 3], V. GASBARRO [3, 4], G. BUFFONE [1]
M. AMATO [2], L. GALLELLI [3], R. SERRA [1, 3], S. DE FRANCISCIS [1, 3]

Expert Opin Biol Ther. 2006 Mar;6(3):257-79.

Antiprotease therapy in cancer: hot or not?

Lah TT[1], Durán Alonso MB, Van Noorden CJ.

Post Thrombotic Syndrome and MMPs levels

- Predicting those patients with acute DVT who may develop PTS, in particular in the early stage, is important for focusing aggressive therapy such as pharmacomechanical thrombolysis (PMT) to maximize benefit to risk and therapeutic success.

Thrombosis Research 134 (2014) 369–375

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

Regular Article

Biomarkers for post thrombotic syndrome: A case-control study

A.C. Bouman [a,c,*], Y.W. Cheung [b], H.M. Spronk [a], C.G. Schalkwijk [c], H. ten Cate [a,c], M. ten Wolde [b], A.J. ten Cate-Hoek [a,c]

Biomarkers: patients (cases and controls) versus healthy individuals.

Markers	Patients (cases and controls) (n = 53) Median (IQR)	Healthy individuals (n = 26) Median (IQR)
Coagulation and fibrinolysis		
APC-ratio*	3.4 (2.6-3.6)	3.5 (2.9-3.9)
D-dimer (ng/mL)*	570 (340-950)	385 (235-513)
PAI (ng/mL)	0.04 (0.04-0.05)	0.04 (0.04-0.17)
PAP (ng/mL)	303.0 (267.0-371.9)	299.2 (260.7-369.4)
proTAFI (%)	96.8 (86.5-108.3)	111.1 (96.1-127.0)
TAT (μg/L)*	2.0 (0.8-3.6)	1.4 (0.4-2.3)
tPA (ng/mL)	8.7 (6.0-10.5)	6.6 (5.1-8.7)
Inflammation		
CRP (μg/mL)	1.8 (0.9-3.4)	2.9 (1.0-6.0)
Il-6 (pg/mL)	1.6 (1.2-2.6)	1.3 (0.9-1.8)
Il-8 (pg/mL)	3.1 (2.3-4.3)	3.2 (2.5-3.8)
Tissue remodelling		
MMP-9 (ng/mL)	42 (32-59)	38 (22-51)
Adhesion and endothelial function		
P-selectin (ng/mL)	39 (32-53)	44 (36-51)
sICAM-1 (ng/mL)	274 (243-328)	271 (234-313)
sVCAM-1 (ng/mL)	433 (383-547)	396 (327-479)
TM (ng/mL)	4.1 (3.7-5.2)	3.7 (3.2-4.1)
vWF (%)	184 (151-226)	145 (89-193)

- Patients with PTS displayed increased coagulation activity, an altered pattern of fibrinolytic marker expression, and increased endothelial activation.

Current management of Post-Thrombotic Syndrome

- ***Compression therapy***, either obtained with short stretch bandages, adhesive bandages, multiple layer bandages (with orthopedic wool plus compressive layers), stockings or zinc bandages. Effective compression therapy is obtained with implements exerting 35–40 mmHg pressure at the ankle.
- ***Medical therapy***: oxpentifylline, aspirin, intravenous prostaglandin E1, sulphydril-containing agents (DL-cysteine or DL-methionine), radical scavengers (allopurinol or dimethyl sulfoxide), and sulodexide. Stanozolol plus elastic stockings might be associated with higher healing rates of lipodermatosclerosis and o-(b-hydroxyethyl)-rutosides might reduce edema and other PTS symptoms.
- ***Surgery:*** when venous ulcers cannot be managed by conservative treatment. Subfascial perforator legation and valvuloplasty appear to be the most promising; deep (femoral-popliteal) valve reconstruction surgery performed after unsuccessful endoscopic perforator surgery, and correction of superficial venous reflux.

AHA Scientific Statement

The Postthrombotic Syndrome: Evidence-Based Prevention, Diagnosis, and Treatment Strategies

A Scientific Statement From the American Heart Association

Susan R. Kahn, MD, MSc, FRCPC, Chair; Anthony J. Comerota, MD; Mary Cushman, MD, MSc, FAHA; Natalie S. Evans, MD, MS; Jeffrey S. Ginsberg, MD, FRCPC; Neil A. Goldenberg, MD, PhD; Deepak K. Gupta, MD; Paolo Prandoni, MD, PhD; Suresh Vedantham, MD; M. Eileen Walsh, PhD, APN, RN-BC, FAHA; Jeffrey I. Weitz MD, FAHA; on behalf of the American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing

Circulation. 2014;130:1636-1661

MMPs Adapted Treatment

Tomorrow
Predictive -test

DVT

High MMPs levels

Low MMPs levels

DVT
Treatment &
Prophylaxis

PE Treatment

PTS

Follow-up

J Thromb Haemost. 2014 Dec 15. doi: 10.1111/jth.12814. [Epub ahead of print]

Inflammation Markers and Their Trajectories after Deep Vein Thrombosis in relation to Risk of Postthrombotic Syndrome.

Rabinovich A[1], Cohen JM, Cushman M, Wells PS, Rodger MA, Kovacs MJ, Anderson DR, Tagalakis V, Lazo-Langner A, Solymoss S, Miron MJ, Yeo E, Smith R, Schulman S, Kassis J, Kearon C, Chagnon I, Wong T, Demers C, Hanmiah R, Kaatz S, Selby R, Rathbun S, Desmarais S, Opatrny L, Ortel TL, Ginsberg JS, Kahn SR.

PTS: if You know it, You will avoid getting it!
...and it will be sustainable in care

- www.unicz.it/cifl/
- www.collegioitalianodiflebologia.it/web/ita/


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