Understanding thrombosis in ACS

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WE ARE THE ESC

Thrombosis
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

Conflicts of interest

- **AstraZeneca, Aspen and Bayer (Speakers fee).**

RDC: ESC Course 2014

- We live with atherosclerosis
- We die of thrombosis

The New England
Journal of Medicine

Volume 303 OCTOBER 16, 1980 Number 16

PREVALENCE OF TOTAL CORONARY OCCLUSION DURING THE EARLY HOURS OF TRANSMURAL MYOCARDIAL INFARCTION

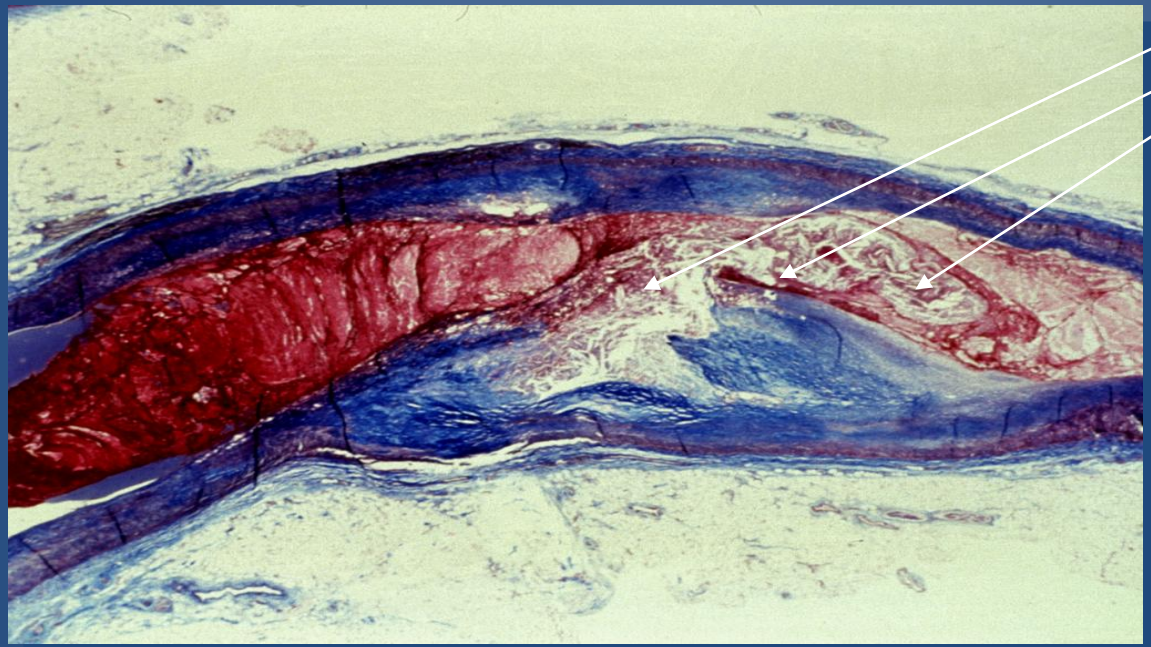
MARCUS A. DEWOOD, M.D., JULIE SPORES, C.R.N.A., ROBERT NOTSKE, M.D., LOWELL T. MOUSER, M.D., ROBERT BURROUGHS, M.D., MICHAEL S. GOLDEN, M.D., AND HENRY T. LANG, M.D.

N Engl J Med. 1980 Oct 16;303(16):897-902.

Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction

DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT

Acute myocardial infarction: coronary thrombus



E Falk 1983 and 1985

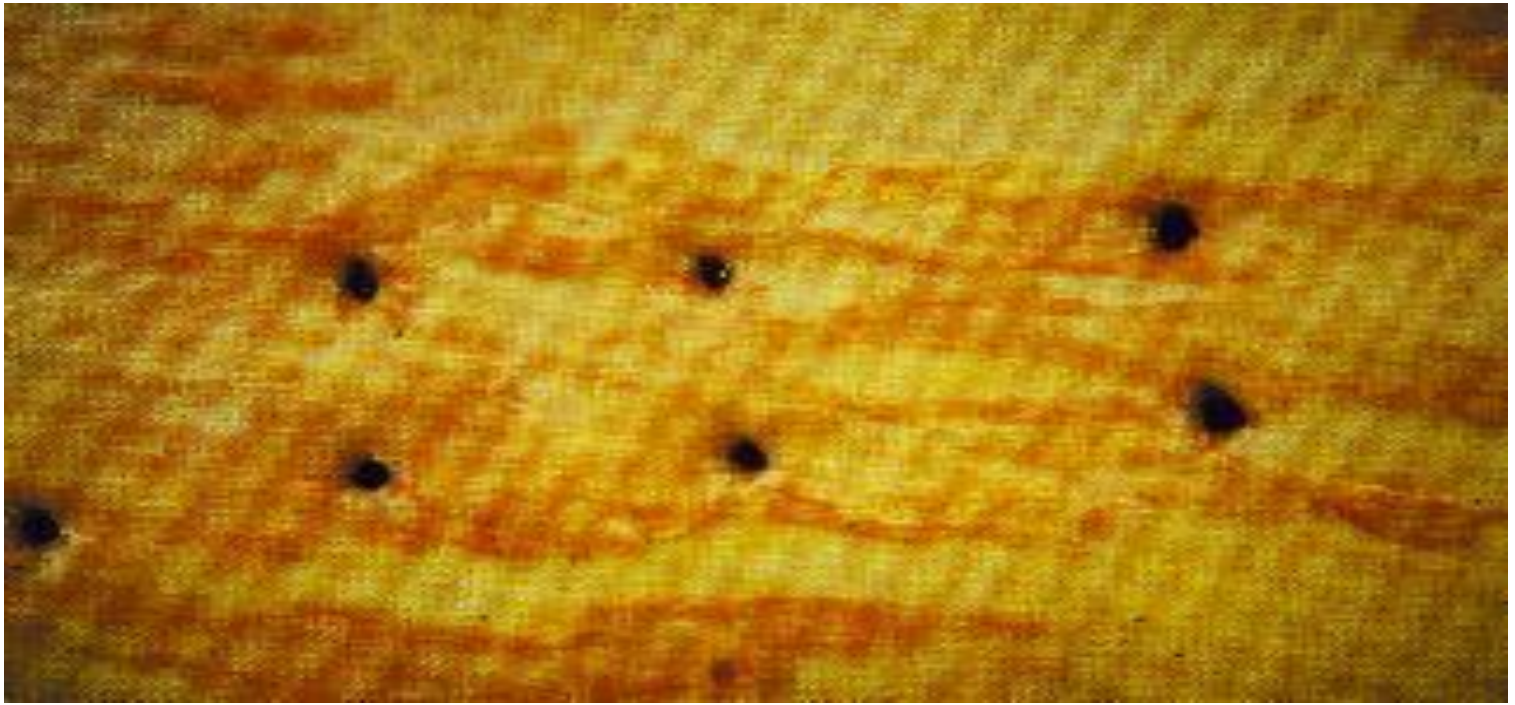
Understanding thrombosis in ACS

- The coronary artery
- Platelets
- Coagulation

Atherosclerosis ➡ atherotrombosis

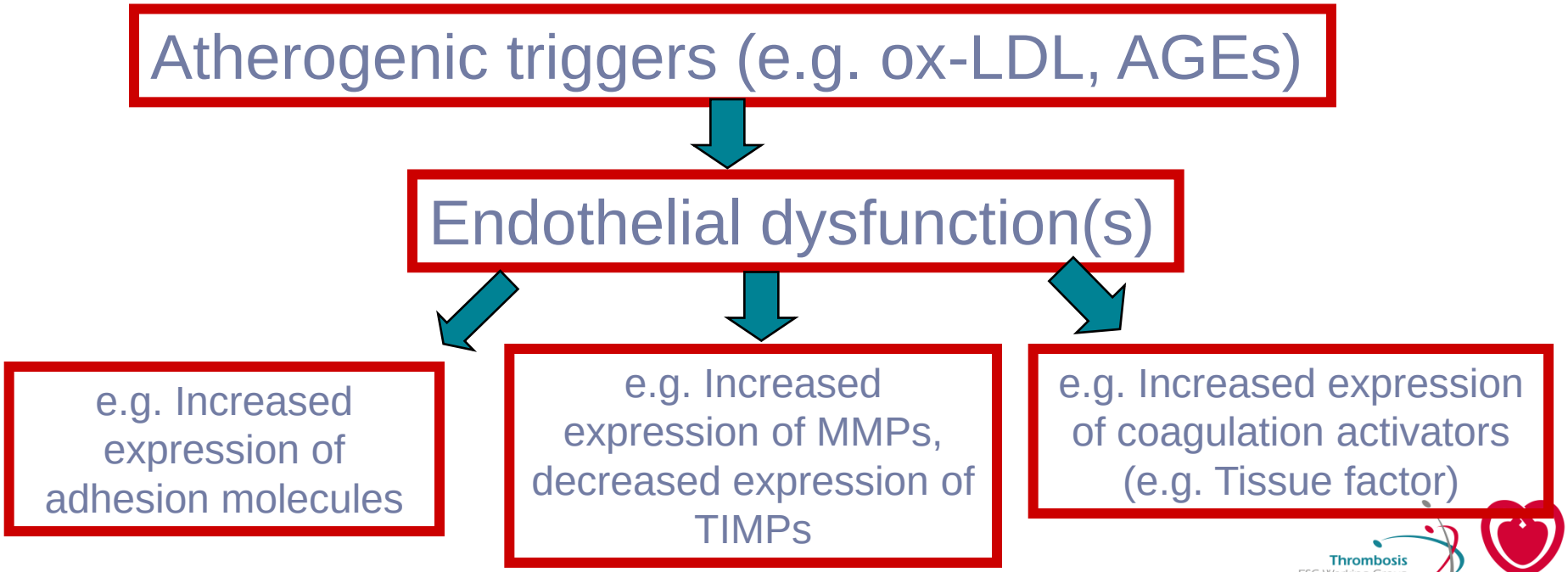
- Inception – the early lesion
- Development – the plaque
- Clinical emergence – plaque rupture and thrombosis

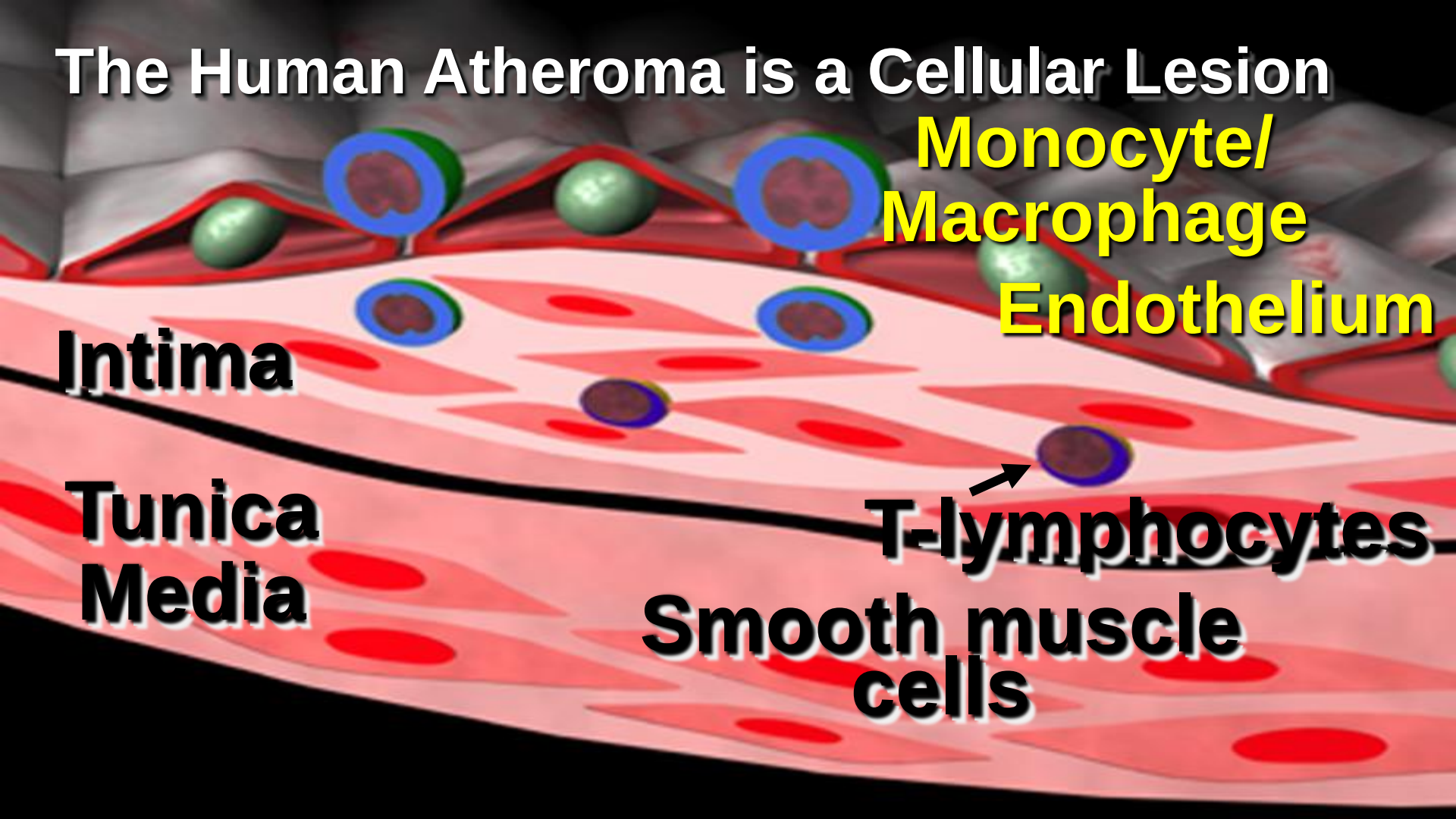
Fatty streak:
the beginning of the story



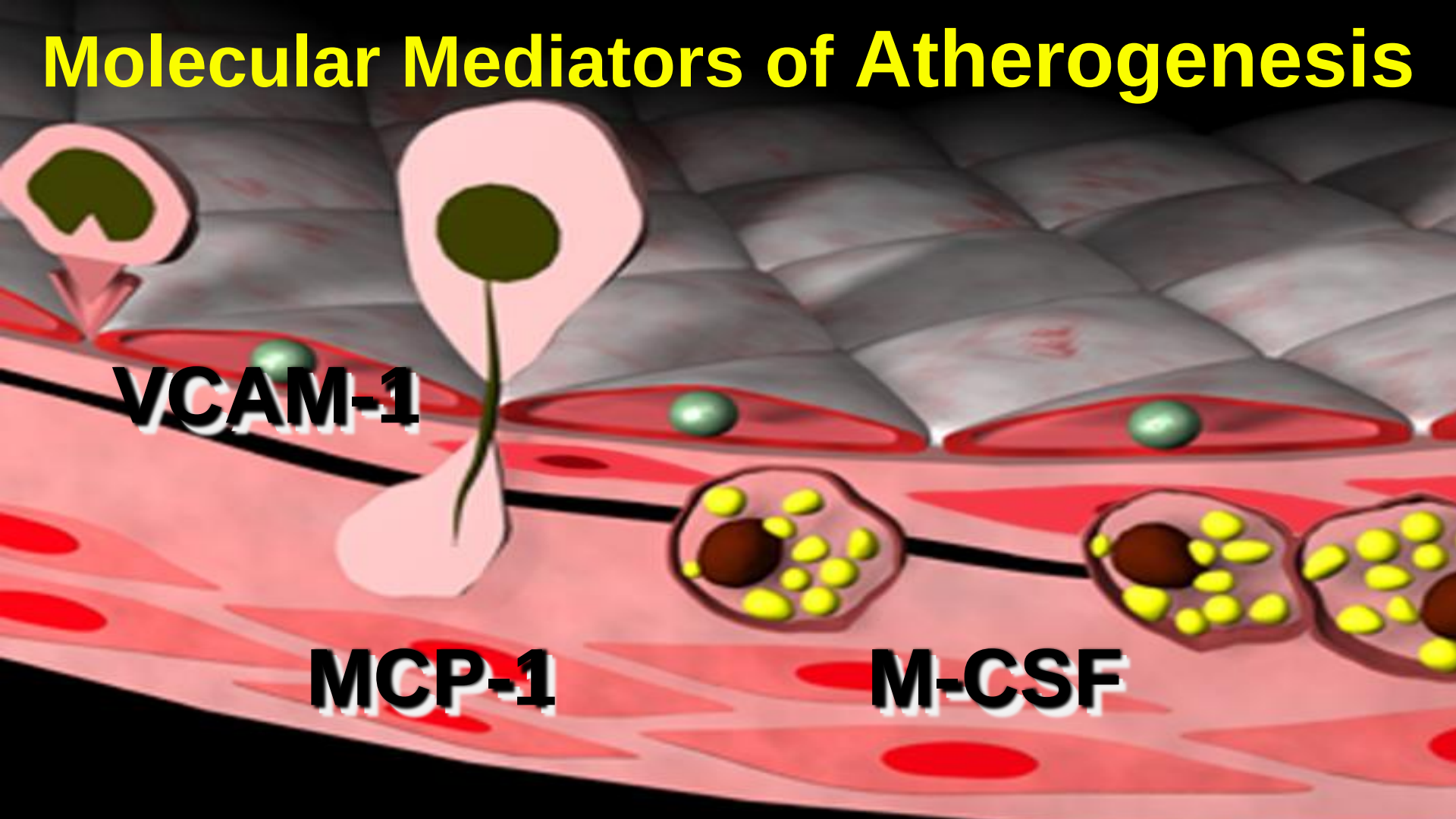
Davies MJ, 1986

Endothelial Dysfunction(s) as a common mechanism in atherothrombosis




The Human Atheroma is a Cellular Lesion
Monocyte/
Macrophage
Endothelium
Intima
Tunica
Media
T-lymphocytes
Smooth muscle
cells

Molecular Mediators of Atherogenesis



Thromb Haemostasis 2016; 116: 2012-21

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Review Article

Inflammation and thrombosis – testing the hypothesis with anti-inflammatory drug trials

Raffaele De Caterina[1]; Emilia D'Ugo[1]; Peter Libby[2]

[1]"G. d'Annunzio" University and Center of Excellence on Aging, Chieti, Italy; [2]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Inflammation and thrombosis

Table 1: Direct mechanisms of inflammation-induced thrombosis (37).

Endothelial cell dysfunction and activation
Platelet activation
Modulation of plasma coagulation
Augmented pro-coagulant functions – Tissue Factor-mediated activation of coagulation
Reduction of endogenous anticoagulants: Antithrombin, Tissue Factor pathway inhibitor (TFPI); Protein C pathway
Inhibition of fibrinolytic activity
Hyperfibrinogenaemia

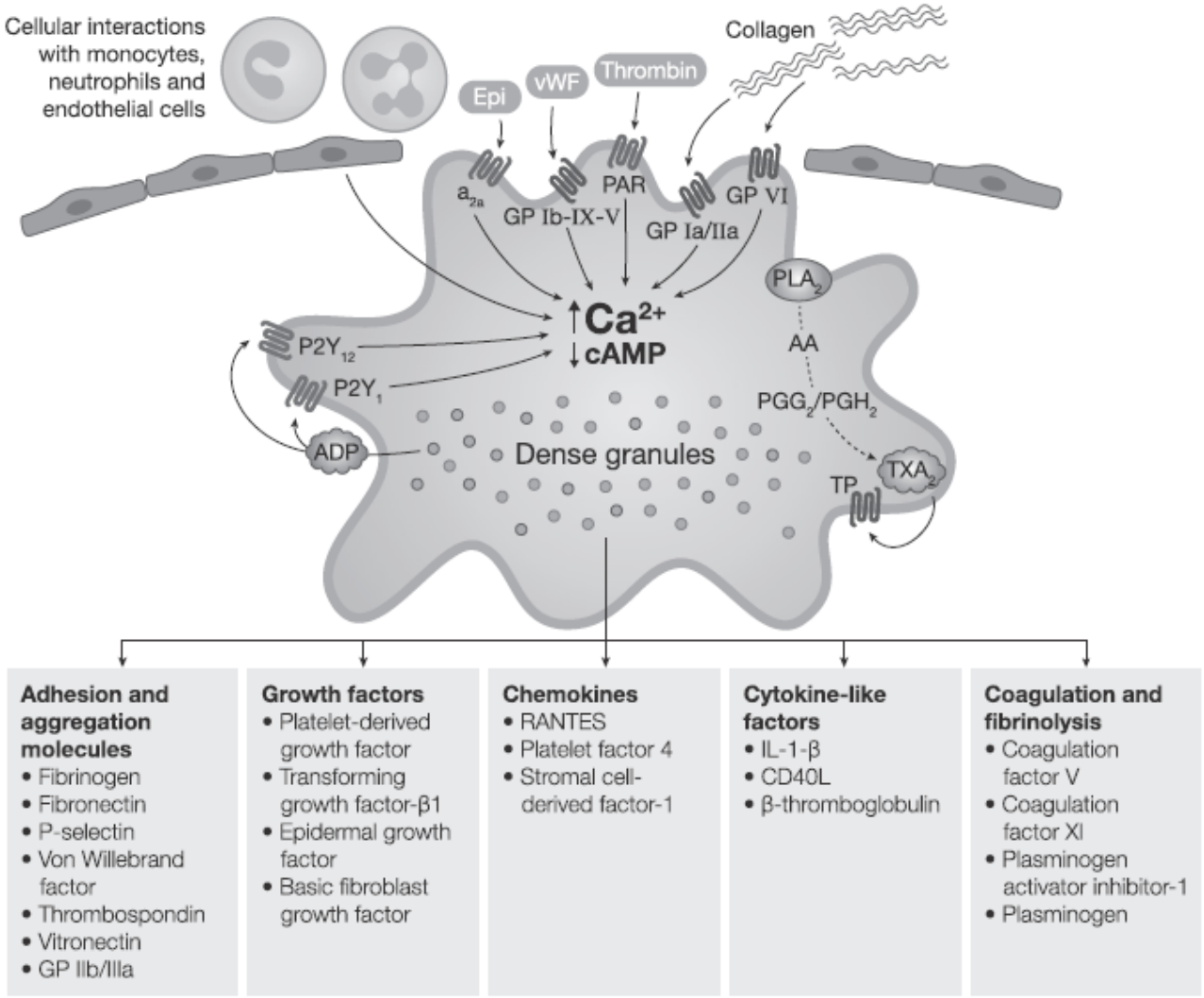
Thromb Haemostas 2015; 114: 519-29

Theme Issue Article

The influence of low-grade inflammation on platelets in patients with stable coronary artery disease

Sanne Bøjet Larsen[1]; Erik Lerkevang Grove[1]; Morten Würtz[1]; Søs Neergaard-Petersen[1]; Anne-Mette Hvas[2,3]; Steen Dalby Kristensen[1,3]

[1]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark; [3]Faculty of Health Sciences, Aarhus University, Aarhus, Denmark



Atherosclerosis revisited from a clinical perspective: still an inflammatory disease?

Donato Santovito[1]; Christian Weber[1,2]

[1]Institute for Cardiovascular Prevention (IPEK), Ludwig-Maximilians-University (LMU) Munich, Munich, Germany; [2]German Centre for Cardiovascular Research (DZHK), partner site Munich Heart Alliance, Munich, Germany

Summary

Compelling experimental results have substantiated the immune-driven inflammatory nature of atherosclerosis. Most of the scientific advances over the past decades have been achieved by relying on transgenic animal models that have been employed with increasing levels of sophistication. However, recent failures in translating various anti-inflammatory therapeutic strategies for use in humans might raise some skepticism with regards to an inflammatory causality underlying human atherosclerosis. By applying a dialectical approach, this *Perspective* aims to challenge and deduce the nature of atherosclerosis by reviewing results exclusively derived from human studies and recent clinical trials, as "things may not always be, what they appear".

Keywords

Inflammation, atherosclerosis, atherothrombosis

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Thromb Haemost 2017; 117: 231–237

Anti-inflammatory strategies in vascular disease

- lowering LDL cholesterol levels below those achievable with statins alone (e.g., inhibition of serum proprotein convertase subtilisin/kexin 9 [PCSK9])
- Colchicine
- darapladib, a small molecular inhibitor of a lipoprotein-associated phospholipase, to reduce clinical events.
- antibody neutralization of the proinflammatory cytokine interleukin-1β
- low-dose methotrexate on a weekly basis
- n-3 fatty acids
- other drugs

Anti-inflammatory strategies in vascular disease

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- antibody neutralization of the proinflammatory cytokine interleukin-1β
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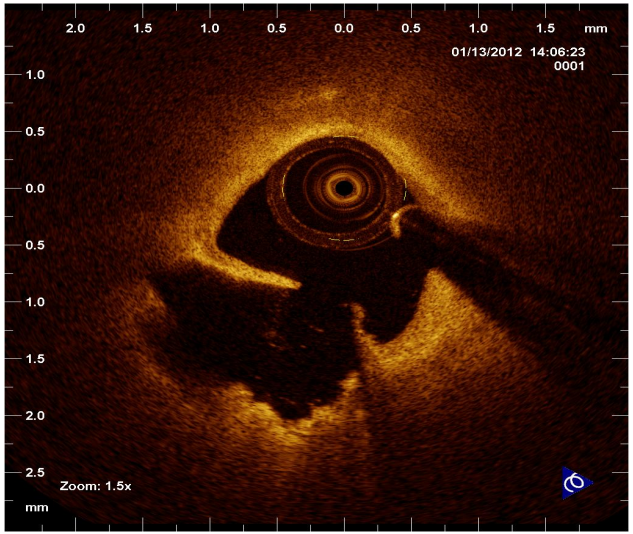
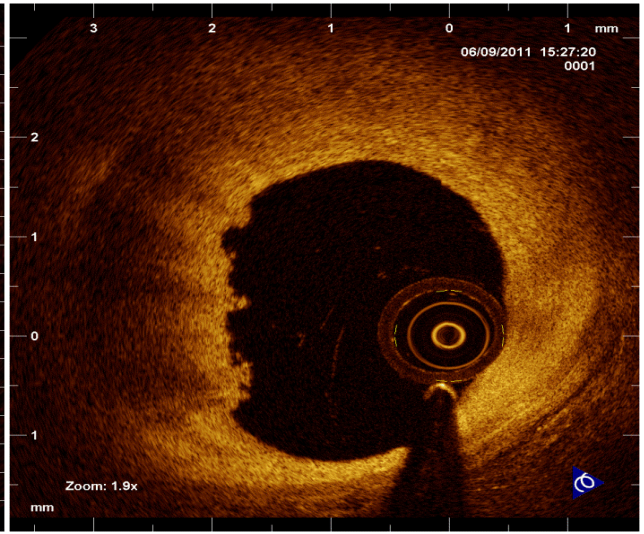
- n-3 fatty acids ?
- other drugs ?

OCT: the EROSION study

Rupture

Erosion

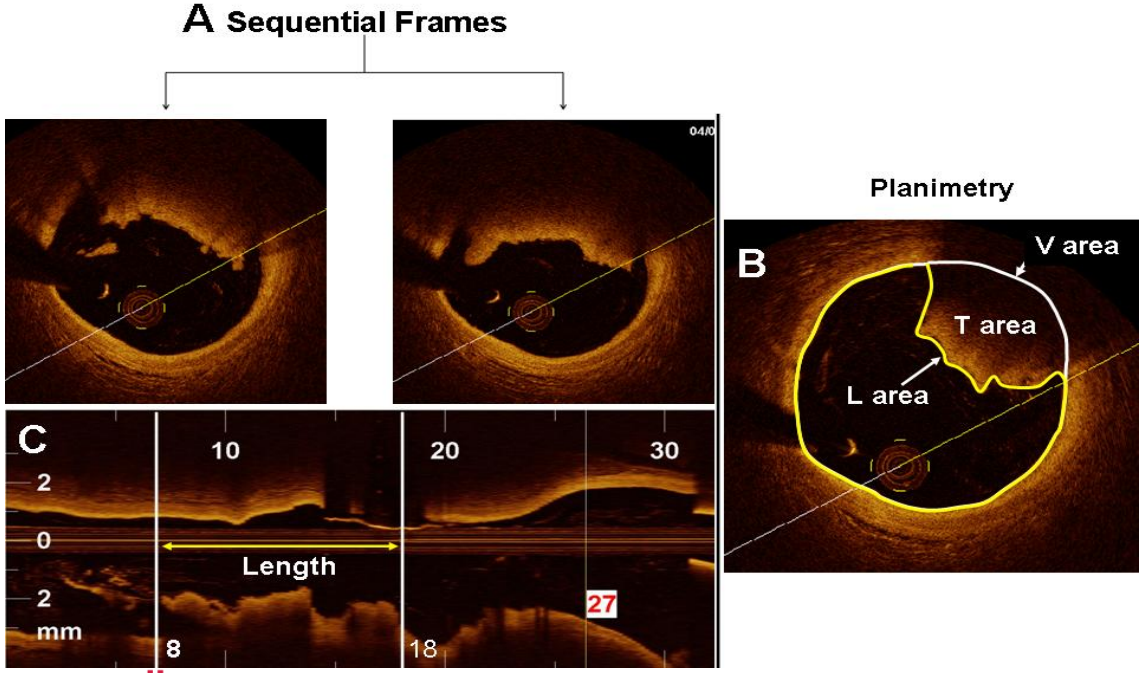




Dr I-K Jang et al

Thrombus Volume Measurement

- Thrombus area was measured on every frame. Thrombus volume was calculated as the sum of thrombus area x thrombus length.



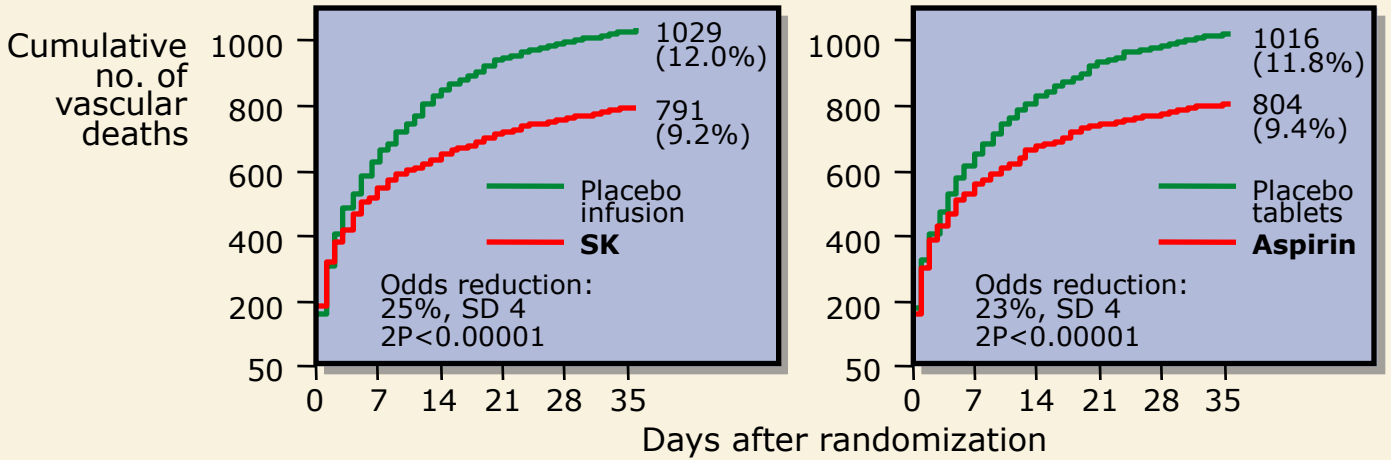
The coronary plaque: 'stabilization'

- **Statins**
- **Stents**

Coronary thrombosis: platelets

ISIS-2: Second International Study of Infarct Survival

Vascular mortality over 35 days: individual therapies



The ISIS-2 collaborative group. *Lancet* 1988; **ii**: 349–60.

Large platelets in acute MI

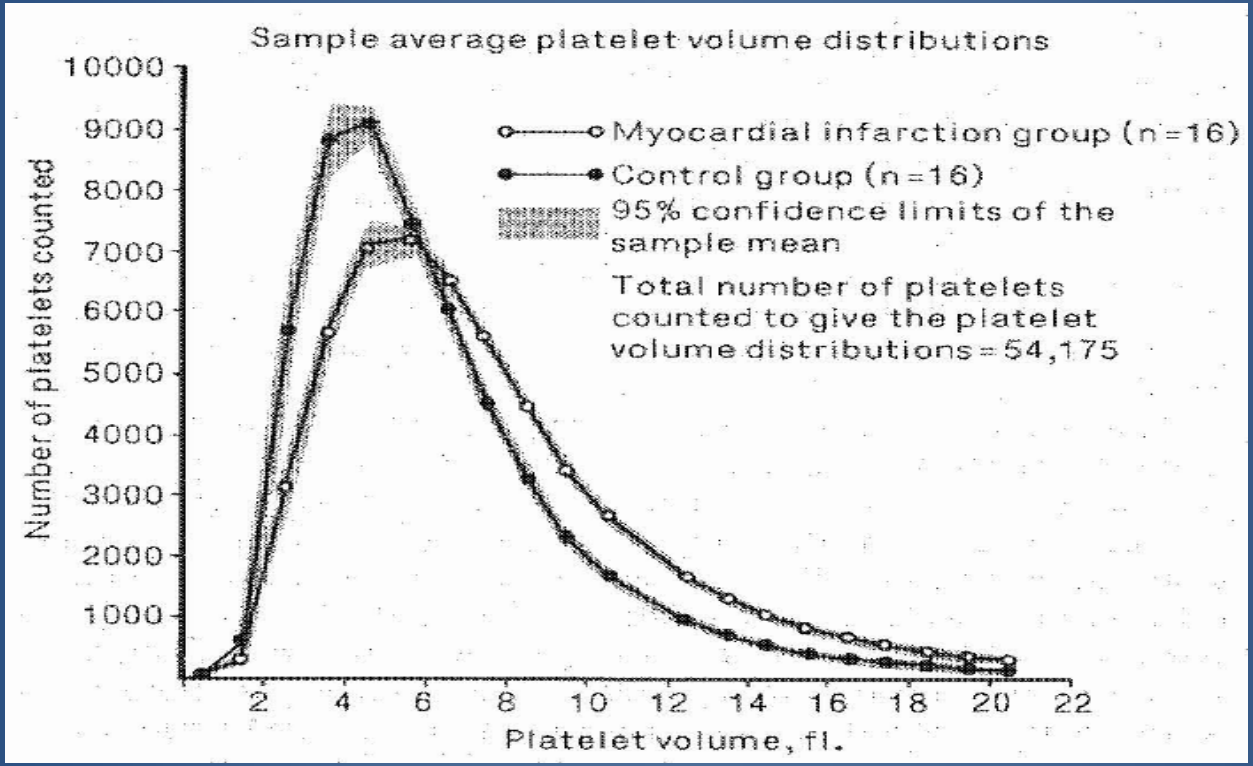
- Increased mean platelet volume in acute MI
- Increased mean platelet volume is a predictor of mortality in patients with acute MI

Martin et al, BMJ 1983

Martin et al, Lancet 1991

Klovaite et al, J Thromb Haemost 2011

Increased platelet volume in acute MI



- Martin et al BMJ 1983, Trowbridge & Martin, Thrombosis and Haemostasis 1987.

The causal role of megakaryocyte–platelet hyperactivity in acute coronary syndromes

John F. Martin, Steen D. Kristensen, Anthony Mathur, Erik L. Grove and Fizzah A. Choudry

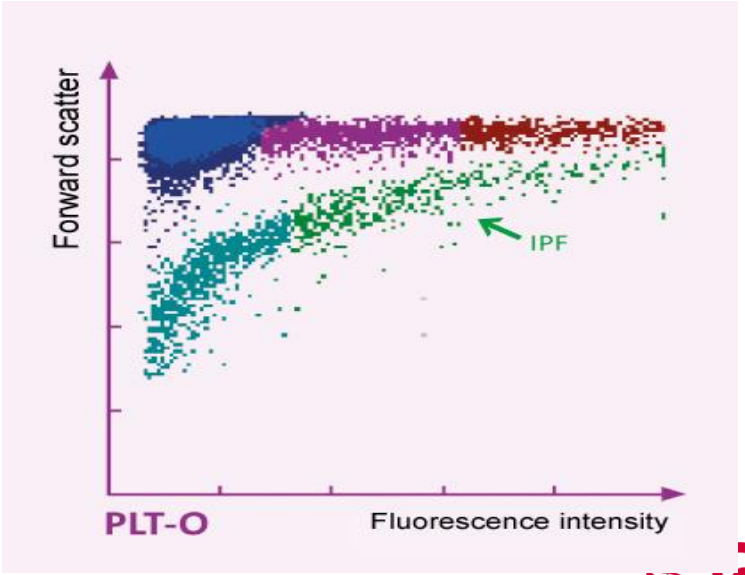
Abstract | Platelets are causally involved in coronary artery obstruction in acute coronary syndromes (ACS). This cell type is unique to mammals and its production, which is unlike that of any other mammalian cell, involves polyploid nuclear change in the mother cell (megakaryocyte) and the production of anucleate cells with a log Gaussian distribution of volume. Platelets vary more in cellular volume than any other circulating blood element in mammals. Larger platelets are denser, contain more secretory granules, and are more reactive than their smaller counterparts. A causal relationship between the presence of large, dense, reactive platelets in the circulation and ACS is supported by many clinical studies. Furthermore, the results of two large, prospective, epidemiological studies have demonstrated that mean platelet volume was the strongest independent predictor of outcome in patients with acute myocardial infarction. Notably, evidence indicates that an increase in mean platelet volume in the pathogenesis of ACS can potentially overwhelm current therapeutics. The control system for the physiological and pathophysiological production of large platelets should, therefore, be researched. An understanding of this system might give rise to new therapeutics that could control platelet reactivity and thereby comprehensively prevent ACS.

Martin, J. F. *et al. Nat. Rev. Cardiol.* advance online publication XX Month 2012; doi:10.1038/nrcardio.2012.131

Platelet production

- Accelerated platelet turnover increase the proportion of newly formed platelets released from megakaryocytes

- Newly formed platelets: higher number of dense granules and increased cell volume



Platelet turnover in ACS

Cardiovascular Biology and Cell Signalling

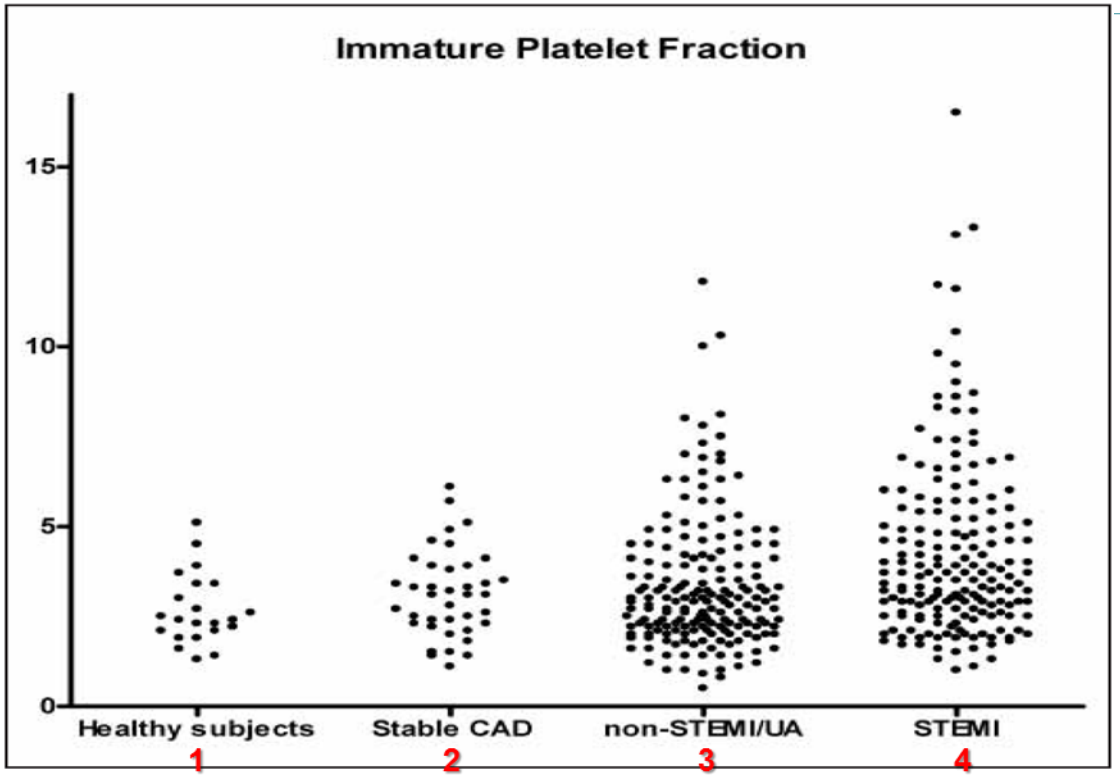
Immature platelets in patients with acute coronary syndromes

Erik Lerkevang Grove[1]; Anne-Mette Hvas[2]; Steen Dalby Kristensen[1]

[1]Department of Cardiology, Aarhus University Hospital Skejby, Aarhus N, Denmark; [2]Department of Clinical Biochemistry, Centre for Haemophilia and Thrombosis, Aarhus University Hospital Skejby, Aarhus N, Denmark

Thromb Haemost 2009;101:151-156.

Platelet turnover in ACS



Grove E.L. et al. *Thromb Haemost* 2009.

Platelet production and turnover

European Heart Journal (2015) **36**, 3211–3213
doi:10.1093/eurheartj/ehv366

EDITORIAL

Platelet progenitors: the hidden drug target

Bianca Rocca and Carlo Patrono*

Department of Pharmacology, Catholic University School of Medicine, Rome, Italy

Online publish-ahead-of-print 1 August 2015

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Comparison of Immature Platelet Count to Established Predictors of Platelet Reactivity During Thienopyridine Therapy

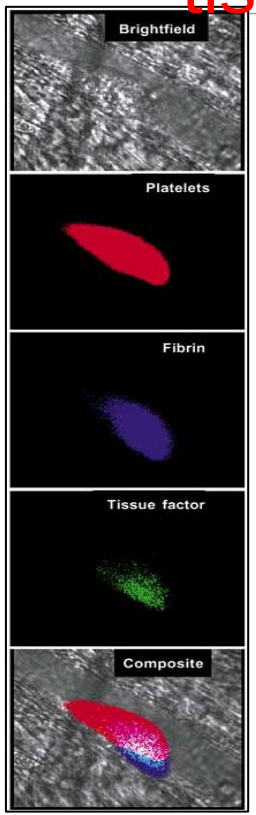
Christian Stratz, MD,[a] Timo Bömicke, MD,[a] Iris Younas, MS,[a] Anja Kittel, PhD,[b] Michael Amann, MD,[a] Christian M. Valina, MD,[a] Thomas Nührenberg, MD,[a] Dietmar Trenk, PhD,[a] Franz-Josef Neumann, MD,[a] Willibald Hochholzer, MD[a]

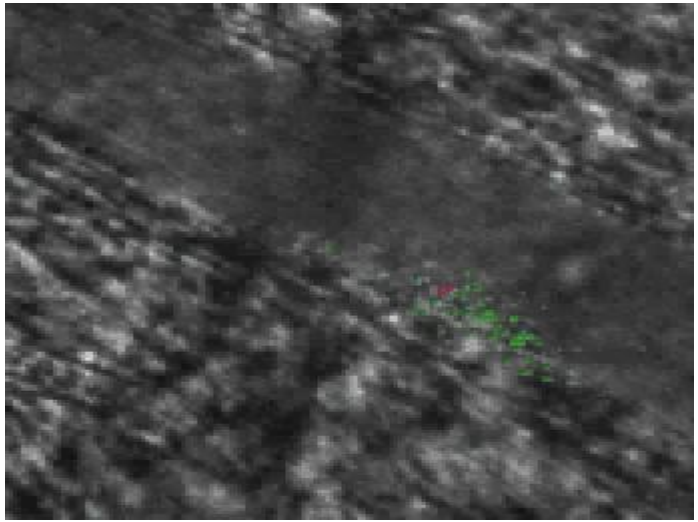
Atherothrombosis: platelet inhibition works

- **Aspirin**

- **Clopidogrel**
- **Prasugrel**
- **Ticagrelor**

In vivo arterial thrombosis involves platelet aggregation, tissue factor generation and fibrin formation





Real-time *in vivo* imaging of arterial thrombus formation in the mouse after laser-induced vascular injury, showing:

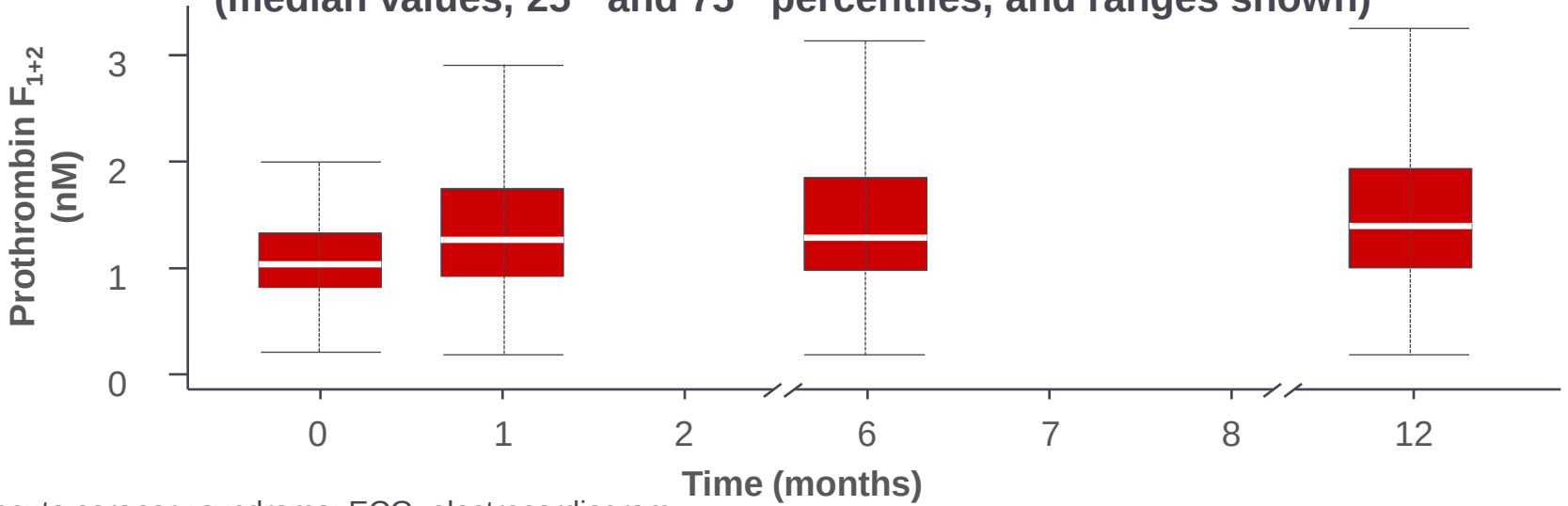
- platelet deposition,
- tissue factor accumulation
- subsequent fibrin generation

Falati *et al*. *Nat Med* 2002;8:1175–81.

Persistently elevated thrombin levels -12 months after an ACS event

- Italian GUSTO IIb trial: 319 patients with ACS; symptoms of cardiac ischaemia at rest ≤12 hours before enrolment and ECG signs of acute ischaemia
- Prothrombin F_{1+2} levels remained elevated at 1, 6 and 12 months after enrolment

Distribution of F_{1+2} values at study beginning (0) and after 1, 6 and 12 months (median values, 25th and 75th percentiles, and ranges shown)



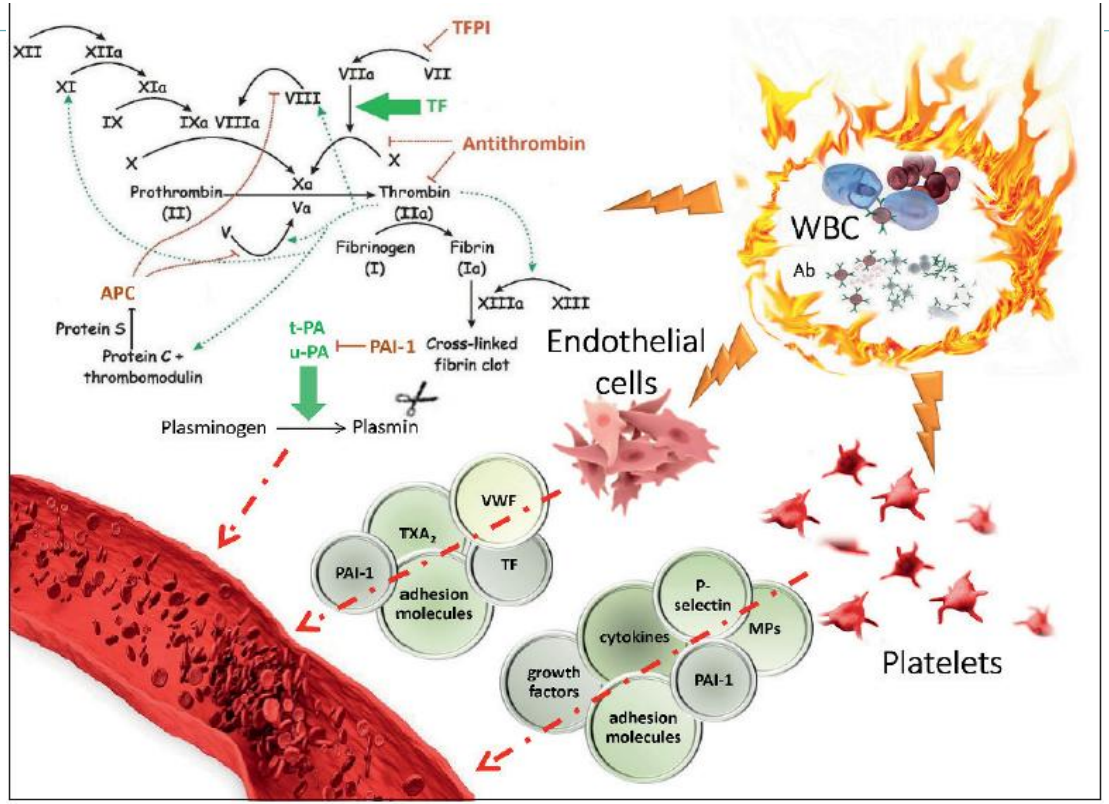
ACS, acute coronary syndrome; ECG, electrocardiogram.

Ardissino *et al*. *Blood* 2003;102:2731–5.

ACS - Anticoagulants work

- Warfarin (WARIS-2)
- Very low dose rivaroxoban (ATLAS TIMI 51)
- UFH, LMWH, fondaparinux, bivalirudin

R De Caterina et al, TH 2016



Atherothrombosis

Atherothrombosis

work hard
stay humble

Steen Husted, died 28th Dec 2016

Speaker