Understanding thrombosis in ACS

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Conflicts of interest

• AstraZeneca, Aspen and Bayer (Speakers fee).
RDC: ESC Course 2014

- We live with atherosclerosis
- We die of thrombosis
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

Atherogenic triggers (e.g. ox-LDL, AGEs)

Endothelial dysfunction(s)

- e.g. Increased expression of adhesion molecules
- e.g. Increased expression of MMPs, decreased expression of TIMPs
- e.g. Increased expression of coagulation activators (e.g. Tissue factor)
The Human Atheroma is a Cellular Lesion

Intima

Tunica Media

Monocyte/Macrophage

Endothelium

T-lymphocytes

Smooth muscle cells

After P. Libby, 2001, with permission
Molecular Mediators of Atherogenesis

VCAM-1

MCP-1

M-CSF
Review Article

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

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Inflammation and thrombosis

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

<table>
<thead>
<tr>
<th>Mechanism</th>
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<td>Endothelial cell dysfunction and activation</td>
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<td>Platelet activation</td>
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<tr>
<td>Modulation of plasma coagulation</td>
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<td>Augmented pro-coagulant functions – Tissue Factor-mediated activation of coagulation</td>
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<tr>
<td>Reduction of endogenous anticoagulants: Antithrombin, Tissue Factor pathway inhibitor (TFPI); Protein C pathway</td>
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<td>Inhibition of fibrinolytic activity</td>
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<td>Hyperfibrinogenemia</td>
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The influence of low-grade inflammation on platelets in patients with stable coronary artery disease

Sanne Bøjet Larsen¹; Erik Lerkevang Grove¹; Morten Würtz¹; Søs Neergaard-Petersen¹; Anne-Mette Hvas²,³; Steen Dalby Kristensen¹,³

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Cellular interactions with monocytes, neutrophils and endothelial cells

Dense granules

Adhesion and aggregation molecules
- Fibrinogen
- Fibronectin
- P-selectin
- Von Willebrand factor
- Thrombospondin
- Vitronectin
- GP Iib/IIa

Growth factors
- Platelet-derived growth factor
- Transforming growth factor-β1
- Epidermal growth factor
- Basic fibroblast growth factor

Chemokines
- RANTES
- Platelet factor 4
- Stromal cell-derived factor-1

Cytokine-like factors
- IL-1β
- CD40L
- β-thromboglobulin

Coagulation and fibrinolysis
- Coagulation factor V
- Coagulation factor XI
- Plasminogen activator inhibitor-1
- Plasminogen

Ca2+ cAMP

P2Y1, P2Y12

ADP

Epi, vWF, Thrombin

GP Ia/IIa, GP Ib-IX-V

GP Ila/IIla

PLA

AA

PGG2/PGH2

TXA

TP

We Are The ESC
Atherosclerosis revisited from a clinical perspective: still an inflammatory disease?

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¹Institute for Cardiovascular Prevention (IPEK), Ludwig-Maximilians-University (LMU) Munich, Munich, Germany; ²German 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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Financial support:
The work of the authors is supported by the Deutsche Forschungsgemeinschaft (SFB1123, A1/B4).

Received: October 10, 2016
Accepted after minor revision: November 10, 2016
Epub ahead of print: December 15, 2016
https://doi.org/10.1160/TH16-10-0770
Thromb Haemost 2017; 117: 231–237

Note: The review process for this manuscript was fully handled by Gregory Y. H. Lip, Editor in Chief.
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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OCT: the EROSION study

Rupture  Erosion

Dr I-K Jang et al

www.escardio.org
Thrombus Volume Measurement

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

A Sequential Frames

B Planimetry

C Length
The coronary plaque: ‘stabilization’

- Statins
- Stents
Coronary thrombosis: platelets
Vascular mortality over 35 days: individual therapies

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

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

John F. Martin, Steen D. Kristensen, Anthony Mathur, Erik L. Grove and Fizah 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
Immature platelets in patients with acute coronary syndromes

Erik Lerkevang Grove¹; Anne-Mette Hvas²; Steen Dalby Kristensen¹

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

Platelet turnover in ACS

Platelet production and turnover

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

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

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, 25$^{th}$ and 75$^{th}$ percentiles, and ranges shown)

ACS: acute coronary syndrome; ECG: electrocardiogram.
ACS - Anticoagulants work

- Warfarin (WARIS-2)
- Very low dose rivaroxoban (ATLAS TIMI 51)
- UFH, LMWH, fondaparinux, bivalirudin
Atherothrombosis
Atherothrombosis
Steen Husted, died 28th Dec 2016