Atherosclerosis: Vaso-vasorum and Plaque Neovascularization

Miodrag Ostojic

Department of Cardiology, Clinical Center of Serbia, Belgrade
The intima of normal coronary arteries lack vasa vasorum, whereas the adventitia and outer media possess a vascular network.

However, studies more than a century described increased number of arterial microvessels in human atheroma.

A reach network of vasa vasorum within human atherosclerotic vessels has been demonstrated.
THE UNITED STATES BELIEVES THAT...

"I KNOW"

BY CHAPPATTE IN "NEZ AM SONNTAG" (ZURICH) GLOBE CARTOON
AGENDA

1. Actuality
2. Definitions and mechanisms of neovascularization
3. History
4. Significance in atherosclerosis
5. Methodology
   5.1 In vitro (in animals and humans)
   5.2 In vivo
6. Improving assessment of CVD risk
7. Therapy
8. Instead of conclusion
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Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)†

Authors/TASK FORCE MEMBERS: William Wijns (Chairperson) (Belgium)*, Philippe Kolh (Chairperson) (Belgium)*, Nicolas Danchin (France), Carlo Di Mario (UK), Volkmar Falk (Switzerland), Thierry Folliguet (France), Scot Garg (The Netherlands), Kurt Huber (Austria), Stefan James (Sweden), Juhani Knuuti (Finland), Jose Lopez-Sendon (Spain), Jean Marco (France), Lorenzo Menicanti (Italy), Miodrag Ostojic (Serbia), Massimo F. Piepoli (Italy), Charles Pirlet (Belgium), Jose L. Pomar (Spain), Nikolaus Reifart (Germany), Flavio L. Ribichini (Italy), Martin J. Schalij (The Netherlands), Paul Sergeant (Belgium), Patrick W. Serruys (The Netherlands), Sigmund Silber (Germany), Miguel Sousa Uva (Portugal), David Taggart (UK)
Long-term Aspirin for Coronary Artery Disease: Are We Being Deceived by a Biased Presentation of the Evidence?

John GF Cleland

Authors and Disclosures


• Aspirin Fallacies: Is there a Sound Biological Rationale for Aspirin?
• Is Long-term Aspirin Therapy Effective?
• Is Aspirin Safe?
• Is the Correct Dose of Aspirin Known?
• Is Aspirin an Appropriate Background Therapy for Other Anti-thrombotic Agents?
• Has the Introduction of New Treatments Altered the Efficacy of Aspirin?
• Inexpensive?
• Is Aspirin Free from Commercial Interest?
Aspirin Fallacies: Is there a Sound Biological Rationale for Aspirin?

All hypotheses depend upon perspective. If coronary events are initiated by platelet aggregation and thrombosis, then it does make sense to use aspirin. On the other hand, if events are triggered by hemorrhage into plaque, an anti-thrombotic agent sounds rather dangerous.

Plaque hemorrhage, rupture and thrombosis are likely to be inextricably intertwined for vascular occlusion-initiating events and plaque hemorrhage may be an important component of plaque growth. There is moderately compelling evidence that low-dose aspirin accelerates the progression of atheroma.[13,14] Once an event has occurred, most patients will develop an ulcerated plaque and thrombus, providing a theoretical substrate for the short-term benefit of aspirin.[15]
Cardiovascular death is at least as common as nonfatal myocardial infarction in these trials, with one notable exception – the US Physicians' Trial.\cite{7} Perhaps aspirin simply conceals nonfatal events or possibly converts some nonfatal events into fatal ones? Many infarcts are not associated with typical symptoms or cause sudden death, and so a modest effect on changing the presentation of symptoms could explain the entire effect of aspirin.\cite{25-28} Those secondary prevention trials that reported it found an increase in sudden death in those who were assigned to aspirin.\cite{19,21,22} Studies with other agents have shown that increasing the risk of sudden death can exert a powerful reduction on the rate of nonfatal myocardial infarction.\cite{29} Recent trials show that approximately half of all myocardial infarctions in patients taking aspirin do not provoke symptoms that bring the patients to hospital acutely.\cite{8,30}
Dear Prof. Patrono,

I did attend the course in Check Republic approximately 10 years were you were a faculty. Since that time I have a great admiration for your work and knowledge. On October 9 2010 in Athens I asked you about Cleland Internet publication (in attachment) where he claimed that Aspirin is harmful promoting bleeding into plaque through vasa vasorum. He claimed that all anti platelets studies excluded pts with sudden death, so metaanalysis was in favor of anti platelets. As I am Chairman and speaker at one session at the Euroecho in Copenhagen on December 9 2010 I have to give talk on Atherosclerosis: Vasa vasorum and neovascularization. I am not aware that anybody contradict that Cleland statements and would like to have your comment on that issue. It will be very useful for me in preparing that talk as well as to realize what is the truth regrading metaanalysis.

Thanks a lot in advance and excuse me for taking a freedom to ask you might be difficult and sensitive question.

Best rgds

Misha
Dear Misha,

thank you for your kind message. As you can read in the attached ATT publication, sudden death was included in this meta-analysis of both primary and secondary prevention aspirin trials. Moreover, aspirin is the only antiplatelet agent (and one of very few cardiovascular drugs) for which there is at least one very large, placebo-controlled randomized trial having vascular mortality as the primary end-point, ie ISIS-2, that shows very clear and statistically robust evidence of a mortality reduction.

With best wishes,

Carlo Patrono
Dear professor Cleland,

I have a great admiration for your work since early Carvedilol studies.

I read your article

Long-term Aspirin for Coronary Artery Disease: Are We Being Deceived by a Biased Presentation of the Evidence?
John GF Cleland

I have not found that anybody contradicted your statements. Since I have invited talk at Evroecho on December 9 2010 on Atherosclerosis: Vasa vasorum and neovascularization I would like to quote your above mentioned publication,

I asked Prof. Carlo Patrono (his e-mail below) if sudden death was included in ATT publication and his reply was affirmative.

In order to have better understanding of your comments I am taking liberty to send you this e-mail. I hope that you may give me some hints in that controversy.

Thanks a lot in advance,

Best rgds

Misha
Thank you.

ISIS-2 lasted 5 weeks. It is likely that aspirin was stopped as this was a double-blind study and in a previous study (ISIS-1) only 5% of patients were given anti-platelet agents. ISIS-2 suggest that 5 weeks of aspirin may deliver a mortality benefit for 10 years! So, it is a great acute therapy but there is no evidence that continuing an anti-platelet agent for more than a few weeks after an event is beneficial. Indeed, there is evidence that the longer the duration between event and starting aspirin, the smaller the benefit and at least two other VA studies have shown no adverse effect from aspirin withdrawal (unstable angina and CABG trials).

I too worry about the role of neo-vascularisation and plaque haemorrhage. Here too aspirin may be a two-edged sword – reducing neo-vascularisation but increasing the risk of haemorrhage. Cardiologists are too stuck on thrombosis and have not considered the contribution of plaque haemorrhage to myocardial infarction and sudden death.

John
Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials

Peter M Rothwell, F Gerald R Fowkes, Jill F F Belch, Hisao Ogawa, Charles P Warlow, Tom W Meade

Summary

Background Treatment with daily aspirin for 5 years or longer reduces subsequent risk of colorectal cancer. Several lines of evidence suggest that aspirin might also reduce risk of other cancers, particularly of the gastrointestinal tract, but proof in man is lacking. We studied deaths due to cancer during and after randomised trials of daily aspirin versus control done originally for prevention of vascular events.

Methods We used individual patient data from all randomised trials of daily aspirin versus no aspirin with mean duration of scheduled trial treatment of 4 years or longer to determine the effect of allocation to aspirin on risk of cancer death in relation to scheduled duration of trial treatment for gastrointestinal and non-gastrointestinal cancers. In three large UK trials, long-term post-trial follow-up of individual patients was obtained from death certificates and cancer registries.
# HR for Cancers: Aspirin vs Control

<table>
<thead>
<tr>
<th>Site of primary cancer*</th>
<th>n</th>
<th>0-5 years’ follow-up</th>
<th>≥5 years’ follow-up</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td>23</td>
<td>0.78 (0.27-2.23)</td>
<td>0.64</td>
</tr>
<tr>
<td>Pancreas</td>
<td>45</td>
<td>0.88 (0.44-1.77)</td>
<td>0.73</td>
</tr>
<tr>
<td>Colorectal</td>
<td>54</td>
<td>0.78 (0.39-1.56)</td>
<td>0.48</td>
</tr>
<tr>
<td>Stomach</td>
<td>36</td>
<td>1.85 (0.81-4.23)</td>
<td>0.14</td>
</tr>
<tr>
<td>Other</td>
<td>24</td>
<td>0.67 (0.23-1.99)</td>
<td>0.47</td>
</tr>
<tr>
<td>All</td>
<td>182</td>
<td>0.96 (0.67-1.38)</td>
<td>0.81</td>
</tr>
<tr>
<td>Non-gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>198</td>
<td>0.92 (0.65-1.30)</td>
<td>0.65</td>
</tr>
<tr>
<td>Prostate</td>
<td>37</td>
<td>0.70 (0.29-1.73)</td>
<td>0.44</td>
</tr>
<tr>
<td>Bladder and kidney</td>
<td>31</td>
<td>1.04 (0.44-2.47)</td>
<td>0.93</td>
</tr>
<tr>
<td>Other solid</td>
<td>93</td>
<td>0.86 (0.52-1.44)</td>
<td>0.57</td>
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<tr>
<td>All</td>
<td>359</td>
<td>0.90 (0.69-1.16)</td>
<td>0.41</td>
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<tr>
<td>Unknown primary</td>
<td>36</td>
<td>0.56 (0.28-1.15)</td>
<td>0.12</td>
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<tr>
<td>All solid cancers</td>
<td>577</td>
<td>0.88 (0.72-1.08)</td>
<td>0.22</td>
</tr>
<tr>
<td>Histological type†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>247</td>
<td>0.86 (0.62-1.18)</td>
<td>0.34</td>
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<tr>
<td>Non-adenocarcinoma</td>
<td>224</td>
<td>0.89 (0.65-1.23)</td>
<td>0.48</td>
</tr>
<tr>
<td>Unknown</td>
<td>106</td>
<td>0.91 (0.58-1.44)</td>
<td>0.70</td>
</tr>
<tr>
<td>Haematological</td>
<td>50</td>
<td>0.82 (0.44-1.54)</td>
<td>0.53</td>
</tr>
<tr>
<td>All cancers‡</td>
<td>627</td>
<td>0.88 (0.72-1.06)</td>
<td>0.17</td>
</tr>
<tr>
<td>All cancers including ETDRS‡</td>
<td>657</td>
<td>0.86 (0.71-1.04)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

The numbers of cancer deaths included from each trial are those shown on webappendix p 3. n = number of cancer deaths. HR = hazard ratio. ETDRS = Early Treatment Diabetic Retinopathy Study. * Analysis confined to the six trials with site-specific cancer data follow-up. † Analysis confined to solid (non-haematological) cancers. ‡ Analysis included cancer deaths in ETDRS, in which neither primary site nor histological type was known in any case.

Rotwell PM, et al, Lancet 2010
Vasa vasorum ("bridging" collaterals and CTO)

Unsuccessful PCI due to subintimal guidewire placement
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Definitions

- **Neovascularization** is the formation of functional microvascular networks with red blood cell perfusion from PEC and/or EC leading to tube formation i.e., stabilized neovascular channel.
- This is a normal process in growth and development, as well as in wound healing.
- However, this is also a fundamental step in the transition of tumors from a dormant state to a malignant state.

**Angiogenesis** is the predominant form of neovascularization in atherosclerosis mediated by EC sprouting from postcapillary venules leading primarily to new capillaries. The network is fragile and prone to rupture since no surrounding mural cells are in place.

**Arteriogenesis** is the structural enlargement by growth of preexisting arteriolar connections often used to establish true collateral circulation.
Mechanisms of vessel wall neovascularization

Pro-angiogenic growth factor expression

- Simuli
  - Medial hypoxia
  - Inflammation
  - Hypertension
  - Oxidative stress
  - Nicotine

Sources
- Vascular SMCs
- Platelets
- Leucocytes
- Plaque
- Microvascular endothelium
- Extracellular matrix
- Vascular progenitor cells

Factors
- VEGF
- PDGF
- FGF
- HGF

Endogenous inhibitors of angiogenesis
- Thrombospondins
- Platelet factor IV
- Endostatin
- Kalistatin
- Collagen XVIII

Downregulation?

NORMAL

ATHEROSCLEROSIS
Why neovessels leak?

- Fragile vessel wall without SMC or pericytes.
- Very large lumen (increased vessel wall stress)
- Lack of supportive extracellular matrix milieu
  - Perivascular inflammation
  - Increased MMP expression
  - Reduced collagen XVII
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Köster - in intimale proliferation associated with the presence of vasa vasorum.

Winternitz injection of Indian ink into the coronary arteries to present the presence of microvascular channels surrounding and penetrating atherosclerotic lesion.

Barger described the presence of vasa vasorum and hemorrhage in atherosclerotic plaques of patients who died from ACS.

Zhang described the positive correlation between intimal thickness (severe stenosis) and extent of neovascularization from VV.

Kumamoto showed vessel lumen as a source of microvessels.

Dvorak increased permeability of atherosclerotic neovessels with gaps between endothelial cells and fenestrated basal membrane, similarly to tumor angiogenesis.

O'Brien described leukocyte infiltration in human coronary plaques as a pathway for leukocyte infiltration in human coronary plaques.

Fryer described intimal neovascularization and intraplaque hemorrhage in atherosclerotic plaques.

Staub VV and neovascularization as predictors of CVD and CV events.

Ritman and Lerman showed difference between adventitial vasa vasorum and atherosclerotic neovessels in structure and response to stimuli.

Magnoni showed correlation between the extent of vasa vasorum and intima-media thickness of human carotid lesions.

Feinstein the first in vivo human study with i.c drug treatment of VV.

Moreno plaque neovascular increased in ruptured atherosclerotic lesion of human aorta.

Stefanadis first men study with i.c drug treatment of VV.

Kumamoto showed positive correlation between the extent of vasa vasorum and intima-media thickness of human carotid lesions.

Zhang described the positive correlation between intimal thickness (severe stenosis) and extent of neovascularization from VV.

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Possible roles of Vasa Vasorum in Coronary Atherosclerosis

Elevated Risk Factors for CAD

Endothelial Dysfunction, Permeability increase

Rate of lipid transport > lipid removal through endothelium via Venous VV

Hypoxia in Arterial Wall

Angiogenesis of VV

Plaque Formation

Cellular Invasion of Wall (Plaque)

Inflammatory Mediators, Oxidative Products

Plaque Calcification

Hemorrhage into Plaque

Stable Plaque

Plaque Rupture

Ritman EL, Lerman A. Cardiovasc Res. 2007; 75: 649-658
AGENDA

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Coronary vasa vasorum neovascularization precedes epicardial endothelial dysfunction in experimental hypercholesterolemia

Joerg Herrmann\textsuperscript{a}, Lilach O. Lerman\textsuperscript{b}, Martin Rodriguez-Porcel\textsuperscript{b}, David R. Holmes Jr\textsuperscript{a}, Darcy M. Richardson\textsuperscript{a}, Erik L. Ritman\textsuperscript{c}, Amir Lerman\textsuperscript{a,*}

\textsuperscript{a}Division of Cardiovascular Diseases, Mayo Clinic Rochester, 200 First Street S.W., Rochester, MN 55905, USA
\textsuperscript{b}Division of Hypertension, Mayo Clinic Rochester, 200 First Street S.W., Rochester, MN 55905, USA
\textsuperscript{c}Department of Physiology and Biophysics, Mayo Clinic Rochester, 200 First Street S.W., Rochester, MN 55905, USA

Received 21 March 2001; accepted 9 May 2001
3D Micro-CT of the LAD in all 3 groups: spatial architecture of vasa vasorum

Group 1 - clear separation of 1st (longitud) and 2nd order VV (circumferenc)

Group 2 and 3 - network of newly formed VV surrounds the host vessel
Vessel wall area in coronary arteries of normal vs animals fed with a high-cholesterol diet


- p<0.001 for all comparisons
- p<0.05 for Group 2 and Group 3 vs Group 1
Endothelium-dependent vasorelaxation of coronary arteries in response to bradykinin

Significant impairment of EDR in animals on 6 and 12 weeks diet vs normal pigs and those on 2 and 4 weeks diet

The current study demonstrates that coronary VV neovascularization occurs within the first 4 weeks of experimental hypercholesterolemia and prior to the development of endothelial dysfunction, a hallmark of the early disease state.

The temporal link may suggest a role for vasa vasorum neovascularization in the initial stage of coronary artery disease.
Arterial Neovascularization and Inflammation in Vulnerable Patients: Early and Late Signs of Symptomatic Atherosclerosis
Michael Fleiner, Marco Kummer, Martina Mirlacher, Guido Sauter, Gieri Cathomas, Reto Krapf and Barbara C. Biedermann

Circulation 2004;110;2843-2850; originally published online Oct 25, 2004;
DOI: 10.1161/01.CIR.0000146787.16297.E8
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539
Autopsy study: Vasa vasorum in symptomatic and asymptomatic pts (n=49)

Adventitial microvessel density per patient in symptomatic vs asymptomatic pts:
33±2 vs 25±2 blood vessels / 1mm²; p=0.008

Adventitial microvessel density in diabetic vs non-diabetic pts:
37±3 vs 29±2 blood vessels / 1mm²; p=0.004

Conclusions

- *in vivo* assessment of arterial intimal thickness, intimal macrophage content, and the intramural microvascular network at several sites of the arterial tree may improve the identification of vulnerable patients.

- The panarterial changes of symptomatic atherosclerosis justify a systemic approach to treat or prevent complicated disease.
Plaque Neovascularization Is Increased in Ruptured Atherosclerotic Lesions of Human Aorta: Implications for Plaque Vulnerability
Pedro R. Moreno, K. Raman Purushothaman, Valentin Fuster, Dario Echeverri, Helena Truszczyńska, Samin K. Sharma, Juan J. Badimon and William N. O’Connor
Circulation 2004;110;2032-2038; originally published online Sep 27, 2004;
DOI: 10.1161/01.CIR.0000143233.87854.23
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75214
Copyright © 2004 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539
Neovascularization and inflammation in 269 human aortic plaques from 24 male pts

Autopsy: Immunohistochemistry, CD34 - positive capillares

Fibro-calcific (n=42)  High-Risk (n=152)  Rupture (n=75)

Neovascularization in human plaques (n=269)

A. Tunica Media

B. Plaque Base

C. Fibrous Cap/Shoulders

D. Total Neovessel Content

Fibro-Calcific (n = 42)  Lipid-Rich (n = 152)  Ruptured (n = 75)
Macrophage quantification score

Score 0
< 5 macs per field

Score 1
6-25 macs per field

Score 2
>25 macs per field

Mild Inflammation

Moderate Inflammation

Severe Inflammation

## Independent Predictors of Plaque Rupture

<table>
<thead>
<tr>
<th>Multivariate Analysis</th>
<th>P value</th>
<th>Odds Ratio</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Cap Thickness &lt; 60 microns</td>
<td>&lt;0.001</td>
<td>23.5</td>
<td>9.3</td>
</tr>
<tr>
<td>Rupture of Internal Elastic Lamina</td>
<td>&lt;0.001</td>
<td>13.7</td>
<td>4.02</td>
</tr>
<tr>
<td>Cap Inflammation Score</td>
<td>0.002</td>
<td>3.12</td>
<td>1.51</td>
</tr>
<tr>
<td>Plaque Base Neovessel Density</td>
<td>0.003</td>
<td>1.47</td>
<td>1.14</td>
</tr>
<tr>
<td>Lipid Area</td>
<td>0.037</td>
<td>1.15</td>
<td>1.01</td>
</tr>
</tbody>
</table>

Conclusions

- Microvessel density was increased in lipid-reach and ruptured plaques when compared with fibrocalcific lesions.
- Lesions with intraplaque hemorrhage and thin fibrous cap also displayed higher microvessel density.
- Microvessel density was low in lesions with mild inflammation and increasingly high in lesions with moderate and severe inflammation.
Microvessels contribute to the phase of repair as a part of cellular inflammatory response to injury.

Neovascularization varies from a transient contribution to healing (wound granulation and regeneration) to a permanent.

Recently, inhibition of angiogenesis by endostatin reduced plaque growth by 70% to 85%, suggesting a role of microvessels in progression of disease.
Atherosclerotic Plaque Progression and Vulnerability to Rupture: Angiogenesis as a Source of Intraplaque Hemorrhage
Renu Virmani, Frank D. Kolodgie, Allen P. Burke, Aloke V. Finn, Herman K. Gold, Thomas N. Tulenko, Steven P. Wrenn and Jagat Narula
*Arterioscler Thromb Vasc Biol* 2005;25;2054-2061; originally published online Jul 21, 2005;
Intraplaque hemorrhage and plaque rupture are associated with increased density of microvessels.

Microvascular disruption may promote lesion progression by erithrocyte-derived holesterol.

This was supported by > 100 cases of sudden coronary death with documented intraplaque VV in ruptured lesions.
TABLE 1. Comparison of Necrotic Core Size, Number of Cholesterol Clefts, Macrophage Infiltration, Number of Vasa Vasorum, and Hemosiderin-Laden Macrophages in Culprit Plaques

<table>
<thead>
<tr>
<th>Plaque Type</th>
<th>Necrotic Core, %</th>
<th>No. Cholesterol Clefts, %</th>
<th>Macrophage Infiltration of Fibrous Cap, %</th>
<th>Mean No. Vasa Vasorum</th>
<th>Mean No. Hemosiderin-Laden Macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupture</td>
<td>34±17*</td>
<td>12±12*</td>
<td>26±20**†</td>
<td>44±22**†</td>
<td>18.9±11**†</td>
</tr>
<tr>
<td>TCFA</td>
<td>24±17</td>
<td>8±9</td>
<td>14±10*</td>
<td>26±23*</td>
<td>4.4±3.6*</td>
</tr>
<tr>
<td>Stable</td>
<td>12±25*</td>
<td>4±6*</td>
<td>3±0.7†</td>
<td>13±9†</td>
<td>5.0±9.3†</td>
</tr>
<tr>
<td>*P value</td>
<td>0.01*</td>
<td>0.04*</td>
<td>0.005*</td>
<td>0.07*</td>
<td>0.001*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.0001†</td>
<td>0.01†</td>
<td>0.03†</td>
</tr>
</tbody>
</table>

Values represent the means±SD.
TCFA indicates thin-cap fibroatheroma (vulnerable plaque).
Modified from Virmani et al. and Kolodgie et al.

- 2 x higher density of VV in vulnerable plaques and 4 x in ruptured plaques

Intraplaque vasa vasorum in coronary artery segment

Multiple branches of VV infiltrate border area of necrotic core
Intraplaque hemorrhage is a critical factor in atherosclerotic plaque growth and destabilization.

The rapid accumulation of erythrocyte membranes causes an acute increase in free cholesterol within the core and excessive macrophage infiltration.

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Carotid Neovessels

Feinstein S. J Am Coll Cardiol. 2006;48:236-43
Human Vasa Vasorum Imaging By Coronary IVUS

Contrast-Induced (Optison)

Vasa Vasorum Detected by Molecular MRI

Targeting $\alpha_v\beta_3$-integrin

Magnetic Resonance Imaging of Intraplaque Hemorrhage (IPH)

Carotid Stenosis 50-79%

Pts without IPH
Pts with IPH

IPH Hazard Ratio: 5.2; (P=.0005)


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Vasa Vasorum and Plaque Neovascularization on Contrast-Enhanced Carotid Ultrasound Imaging Correlates With Cardiovascular Disease and Past Cardiovascular Events

Daniel Staub, Mita B. Patel, Anjan Tibrewala, David Ludden, Mahala Johnson, Paul Espinosa, Blai Coll, Kurt A. Jaeger and Steven B. Feinstein

Stroke 2010;41;41-47; originally published online Nov 12, 2009;
DOI: 10.1161/STROKEAHA.109.560342

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Methodology

- N=147 pts, age 64±11 years
- CECU imaging in vivo
  - Grade 1: no microspheres for VV and
  - Grade 2: yes neovascular.

DEFINITIONS:
- CVD: periferal arterial occlusive disease, coronary artery disease, history of MI, cerebrovascular disease including history of TIA or stroke
- CV events: history of MI, TIA or stroke
Intraplaque neovascularization and plaque in pts

CV events

N=147 pts

Staub D, et al. Stroke 2010;41

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Subjects with CV events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque</td>
<td>8%</td>
</tr>
<tr>
<td>Intraplaque neovasc grade 2</td>
<td>31%</td>
</tr>
<tr>
<td>Intraplaque neovasc grade 2</td>
<td>38%</td>
</tr>
</tbody>
</table>

p=0.012

p=0.031
Univariate and multivariate analysis in pts with history of CVD and events

<table>
<thead>
<tr>
<th></th>
<th>Cardiovascular Disease</th>
<th>Cardiovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95%CI)</td>
<td>P Value</td>
</tr>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>1.09 (1.04–1.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4.5 (1.9–10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.5 (2.2–9.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current or former smoker</td>
<td>1.3 (0.7–2.5)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>0.99 (0.97–1.00)</td>
<td>0.007</td>
</tr>
<tr>
<td>Statins</td>
<td>6.4 (2.4–17.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of plaque</td>
<td>8.3 (3.4–20.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasa vasorum grade 2</td>
<td>2.3 (1.1–4.8)</td>
<td>0.031</td>
</tr>
<tr>
<td>Intraplaque neovascularization grade 2</td>
<td>1.8 (0.8–4.1)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>1.05 (1.00–1.10)</td>
<td>0.046</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.1 (0.8–5.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.5 (1.0–6.3)</td>
<td>0.052</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>1.00 (0.99–1.01)</td>
<td>NS</td>
</tr>
<tr>
<td>Statins</td>
<td>4.8 (1.2–19.4)</td>
<td>0.026</td>
</tr>
<tr>
<td>Presence of plaque</td>
<td>4.7 (1.6–13.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Vasa vasorum grade 2</td>
<td>1.7 (0.7–4.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraplaque neovascularization grade 2</td>
<td>2.0 (0.7–5.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NS, not significant; LDL, low density lipoprotein.

Staub D, et al. Stroke 2010;41
Conclusions

- Pronounced enhancement of adventitial vasa vasorum on CECU was associated with established CVD.
- The presence of vasa vasorum-derived intraplaque neovascularization was associated with a history of CV events (MI, TIA and stroke).
- This supports the concept that intraplaque neovascularization is associated with plaque instability and vulnerability.
AGENDA

1. Actuality
2. Definitions and mechanisms of neovascularization
3. History
4. Significance in atherosclerosis
5. Methodology
   5.1 In vitro (in animals and humans)
   5.2 In vivo
6. Improving assessment of CVD risk
7. Therapy
8. Instead of conclusion
Plaque Neovascularization and Antiangiogenic Therapy for Atherosclerosis

Brendan Doyle, MD,* Noel Caplice, MD, PhD†

Rochester, Minnesota; and Cork, Ireland
Inhibition of angiogenesis

**DRUGS**

1. **Bevacizumab** (Avastin) binds vascular endothelial growth factor (VEGF), inhibiting its binding to the receptors that promote angiogenesis.

- R & D driven to find better cancer treatments.
- Tumors can grow only if they form new blood vessels.
- Stopping the growth of blood vessels may prevent exention of tumors
- In animal studies, angiogenesis inhibitors have successfully stopped the formation of new blood vessels.
Microvascular Normalization: VEGF inhibitor Bevacizumab (Avastin)

- Colon Cancer
- Rectal Cancer
- Breast Cancer
- Renal Cell Cancer
- Esophageal Cancer
- Small Cell Lung Cancer
- Diabetic Retinopathy
- Macular Degeneration
- Coroidal Neovascularization

References:
- Grothey A. Semin Oncol. 2006;33(Suppl 10):S8-S14
- Jain RK. Nat Med. 2003;9:695-93
- Willett CG Semin Oncol. 2006;33(Suppl 10):S35-40
- Jorge R Retina. 2006 November/December;26(9):1006-1013
Inhibition of angiogenesis

**DRUGS**

2. **Talidomide** as an antiangiogenic agent.

- In pregnant women fetus will not form blood vessels properly and thereby stop the proper development of fetal limbs and circulatory systems.

3. **MMP inhibitors** Batimastat and Marimastat.

4. **Cannabinoids**, restrict the sprouting of blood vessels to brain tumors by inhibiting the expression of genes needed for the production of vascular endothelial growth factor (VEGF)

5. **Statins**
Components of human diets also act as mild angiogenesis inhibitors:

- Soy products such as tofu and tempeh, (which contain the inhibitor "genistein")
- Agaricus blazei mushrooms (angiogenesis inhibitors found in the mushroom include sodium pyroglutamate and ergosterol)
- Black raspberry extract (Rubus occidentalis)
- Reishi mushrooms (via inhibition of VEGF and TGF-beta)
- Trametes versicolor mushrooms
- Maitake mushrooms (via inhibition of VEGF)
- Phellinus linteus mushrooms
- Green tea (catechins)
- Liquorice (glycyrrhizic acid)
- Red Wine (resveratrol)
- Bananas produces a substance known as TNF which combats cancer cells
First-in-man Study
Avastin eluting BiodivYsio stent

- 20 patients with recent ACS (<1 month)
- ≥ 2 angiographically significant stenoses (culprit and non-culprit)
- Non-culprit lesion stenoses >50%
- PTCA in culprit vessel
- Avastin eluting BiodivYsio stent deployment in non-culprit vessel *

Follow-up:
- angiographic at 12 months * and
- clinical up to 24 months.

*IVUS of the target vessel was performed immediately after the procedure and at 12 months.

Stefanadis C et al, Atheroscl 2007
Impregnation of drug into the PC coating involves immersing of stent into a standard bevacizumab solution and allowing it to air dry.

Stefanadis C et al, Atheroscl 2007
Local drug delivery

The Drug
Avastin

The Vehicle
BiodivYsio stent

Stefanadis C et al, Atheroscl 2007
First-in-man Study
Avastin eluting BiodivYsio stent

- Clinical follow-up period: 23.54±5.68 months
- Follow-up coronary angiography with QCA and IVUS: 12.03±2.92 months
- Final end points: MACE (death, MI, revascularization)

Stefanadis C et al, Atheroscl 2007
First-in-man Study
Avastin eluting BiodivYsio stent deployment case

Pre

Post

Stefanadis C et al, Atheroscl 2007
First-in-man Study
Avastin eluting BiodivYsio stent
Follow-up angio 1 year

Stefanadis C et al, Atheroscl 2007
The implantation of bevacuzimab-eluting stents (Avastin) in human coronary arteries seems safe and elicits minimal neointimal hyperplasia in the treatment of non-culprit de novo lesions in pts suffering from ACS.

Stefanadis C et al, Atheroscl 2007
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Artificial intelligence
Artificial intelligence:
Need for defined
- fields
- values and
- outcomes