

Supplementary table to Bennett et al. “Peripheral arterial disease and Virchow’s triad“ (Thromb Haemost 2009; 101.6)

Supplementary Table 1: Examples of Recent studies reporting positive associations between components of Virchow’s Triad and peripheral arterial disease

Components of Virchow’s Triad:

A: *Abnormal blood vessel wall*

B: *Abnormal blood constituents*

C: *Abnormal blood flow*

ABPI: ankle brachial pressure index; PAD: peripheral arterial disease; IC: intermittent claudication; CLI: critical limb ischaemia; MI: myocardial infarction; TIA: transient ischaemic attack; CAD: coronary artery disease; AAA: abdominal aortic aneurysm; BMI: body mass index; PTA: percutaneous transluminal angioplasty; TF: tissue factor; TFPI: tissue factor pathway inhibitor; CRP: C-reactive protein; IL: interleukin; VCAM-1: vascular adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; Hcy: homocysteine; PAI-1: plasminogen activator inhibitor-1; tPA: tissue plasminogen activator; TM: thrombomodulin; SAA: serum amyloid A; IMT: intima medial thickness; AIx: aortic index; P-sel: p-selectin; VWF: von Willebrand factor; Lp(a): lipoprotein (a); TAT: thrombin antithrombin three; PMA: platelet microaggregates, MCP-1: monocyte chemoattractant protein-1; PMP: platelet microparticles; WSS: wall shear stress, CEC: circulating endothelial cells; Hct: haematocrit.

Study & Population	Markers Studied	Summary of significant (P<0.5) associations	Components of Virchow’s Triad
Khaleghi et al. 2009 [151] 1051 African Americans, 894 Non-Hispanic Whites	Fibrinogen, d-dimer, Factors V, VII, VIII, VWF, Antithrombin III	Elevated fibrinogen and d-dimer were the only markers independently associated with lower ABPI in African Americans and Non-Hispanic Whites	A, B
Bartlett et al. 2009 [99] 785 men with PAD	Fibrinogen	Baseline fibrinogen was an independent predictor of all-cause mortality risk. Adding fibrinogen to a set of other risk factors did not improve predictive ability.	B
Gosk-Bierska et al. 2008 [152] 62 patients with IC, 20 controls	TF, TFPI	Patients with PAD had higher TF, total TFPI and truncated TFPI than controls. Full-length TFPI was lower in patients with PAD than in controls	A
McDermott et al. 2008 [153] 423 patients with PAD	D-dimer, CRP, IL-6, VCAM-1, ICAM-1, Hcy	Elevated levels of all of these factors were associated with poorer 6 minute walking performance. Increased d-dimer, IL-6, VCAM-1 and Hcy were associated with slower usual paced	A, B

		4 metre walking speed	
Mota et al. 2008 [105] 36 patients with PAD, 30 Controls	D-dimer, plasminogen, prothrombin fragment 1 & 2, PAI-1, TM	Patients had higher levels than controls. Inverse correlations between plasminogen and PAI-1	A, B
Heneghan et al. 2008 [135] 225 patients with CLI undergoing revascularisation procedures	Hcy	Patients with raised Hcy had significantly lower primary, assisted primary and secondary patency rates at all intervals to 36 months. Mean amputation survival was lower in patients with raised Hcy	B
Hogh et al. 2008 [128] 452 patients with symptomatic PAD	CRP	CRP levels were higher overall among patients developing primary endpoints (death, lower limb amputation, peripheral revascularisation) or secondary endpoint (thrombosis of lower limbs, MI, stroke, TIA)	B
Vidula et al. 2008 [154] 377 patients with PAD	D-dimer, CRP, SAA	Higher levels of these factors was associated with higher all cause and higher cardiovascular mortality among patients who died within 1 st 2 years of measurement in people with PAD	B
Sodhi et al. 2007 [155] 195 patients >40 years free from cardiovascular disease and symptomatic PAD	IMT	There was a significant correlation between ABPI and common carotid IMT	A
Khaleghi et al. 2007 [77] 475 Patients with PAD	AIx.	AIx. Was independently associated with lower ABPI; association modified by age	A
Brewer et al. 2007 [78] 106 Patients with PAD	AIx.	High AIx associated with lower walking distance in people with PAD	A
Rajagopalan et al. 2007 [79] 182 patients with symptomatic PAD	P-Sel Fibrinogen	Patients with sub-critical limb ischaemia had significantly enhanced ADP stimulation, P-Sel expression and bound fibrinogen. Also had higher TRAP platelet aggregation	B

<p>Cleanthis et al. 2007[156]</p> <p>19 patients with IC and 10 patients with CLI taking aspirin 12 controls not on aspirin</p>	<p>PMA, P-Sel, MCP-1</p>	<p>P-Sel, PMA and MCP-1 were all higher in CLI compared to IC and controls despite aspirin</p>	<p>B</p>
<p>Tzoulaki et al. 2007[56]</p> <p>1519 men & women</p>	<p>CRP, fibrinogen, Lp(a), Hct, IL-6, ICAM-1, VCAM-1, blood viscosity, plasma viscosity, tPA</p>	<p>CRP, fibrinogen, Lp(a) and Hct were significantly associated with PAD after 17 years follow up. Significant trend between higher levels of ICAM-1, D-dimer, tPA and Hct and worsening disease from no disease to moderate (IC) and severe (CLI or surgical intervention). IL-6, ICAM-1, Lp(a), fibrinogen, tPA and D-dimer and all rheological markers were significantly elevated at baseline in patients who experienced symptomatic PAD during 17 year follow up.</p>	<p>A, B, C</p>
<p>Iwashima et al. 2006[54]</p> <p>40 patients with PAD 48 controls</p>	<p>ICAM-1, VCAM-1, Adiponectin, CRP</p>	<p>Adiponectin was lower in PAD than without. Adiponectin, sICAM-1, sVCAM-1, hsCRP were independently associated with ABPI</p>	<p>A</p>
<p>Allison et al. 2006[125]</p> <p>6814 men and women free from clinically apparent cardiovascular disease</p>	<p>IL-6, fibrinogen, d-dimer, Hcy, VWF</p>	<p>IL-6, fibrinogen, d-dimer and Hcy were all significantly associated with PAD after adjustment for transitional cardiovascular risk factors</p>	<p>A, B</p>
<p>Kals et al. 2006[73]</p> <p>38 Patients with PAD 28 Controls</p>	<p>Arterial elasticity, oxidative stress</p>	<p>Patients with PAD had decreased large and small artery elasticity. Decreased arterial elasticity and high grade oxidative stress was found in patients with atherosclerosis.</p>	<p>A, C</p>
<p>Spring et al. 2006[146]</p> <p>31 Patients with</p>	<p>WSS, erythrocyte aggregation, leucocyte count, fibrinogen, plasma</p>	<p>WSS was lower in patients with PAD and AAA than in controls. WSS was inversely related to erythrocyte aggregation,</p>	<p>A, B, C</p>

PAD 31 patients with AAA 37 Controls	viscosity, IMT	fibrinogen, leucocyte count, plasma viscosity and IMT.	
Brevetti et al. 2006 [157] 154 patients with PAD	CRP, metabolic syndrome	Metabolic syndrome was present in 51.9% of PAD patients. Patients with an ABPI <0.64 were more likely to have metabolic syndrome than those with less severe PAD. PAD patients with metabolic syndrome had higher BMI & CRP than those without.	B
Unlu et al. 2006 [158] 45 patients with PAD 44 controls	D-dimer, CRP, fibrinogen, SAA	D-dimer, CRP, SAA were higher in PAD group than control group. PAD associated with moderately higher fibrinogen. CRP & serum amyloid A had an inverse relationship with ABPI. D-dimer & fibrinogen were related to lower ABPI	B
Kudoh et al. 2006 [85] 42 patients with CAD and PAD 56 CAD only 32 controls	Platelet aggregation	The level of small platelet aggregates was increased significantly in the PAD group compared with both CAD and control groups. Platelet aggregability was increased in patients with PAD with the degree of platelet aggregation being closely related to ABPI	B
Laxdal et al. 2006 [98] 139 vascular interventions on 103 patients with common iliac occlusive disease	Hcy, fibrinogen, d- dimer, activated protein C resistance	There was a significant association between patency rate and levels of fibrinogen, Hcy. The highest values of Hcy and fibrinogen were independent predictors of failure	B
McDermott et al. 2005 [66] 6570 men and women free from clinically evident disease	IMT	Men and women with definite PAD, borderline ABPI or low- normal ABPI had significantly higher internal CIMT than those with normal ABPI. In men the association between ABPI and internal CIMT were significantly less inverse in Caucasians than in African Americans	A
Cassar et al. 2005 [29]	CRP, VWF, d- dimer, TAT	CRP, vWF, d-dimer and TAT were significantly raised in patients with IC compared to	A, B

132 patients with IC 30 CLI 40 controls		controls. Patients with CLI had significantly higher levels of CRP, VWF, and TAT than claudicants	
Sofi et al. 2005 [159] 280 patients with symptomatic PAD 280 controls	PAI-1, Lp(a), Hcy, factor V leiden mutation, prothrombin variant	There was an association between PAD symptoms and prothrombin variant, altered levels of homocysteine, Lp(a), PAI-1 and APA. The presence of Lp(a) and another metabolic antibody increased the risk of PAD symptoms. There was a correlation between the number of altered thrombophilic factors and Fontaine stage of PAD.	B
Tan et al. 2005 [88] 23 patients with CLI 36 with IC 30 controls	Platelets, P-sel, PMP	PMPs were increased relatively to healthy controls in patients with IC and further increased in critical limb ischaemia. Platelets and sP-Sel independently predict PAD severity on multivariate analysis	B
Wildman et al. 2005 [160] 4787 men and women	CRP, fibrinogen, leucocyte count	On multivariate analysis there were significantly higher odds of developing PAD in the highest compared to the lowest quartiles of CRP, fibrinogen and leucocyte count levels	B
Urge et al. 2005 [161] 37 Diabetic patients with PAD	Hct	Increase in claudication distance correlated with haematocrit decrease in diabetic patients with peripheral vascular disease.	C
Makin et al. 2004 [48] 20 patients in each group of ischaemic rest pain, acute MI, stable IC, healthy controls	CEC, TF, VWF	Increased number of CECs and elevated TF and vWF in patients with ischaemic rest pain compared to those with IC and healthy controls.	A
Lee et al. 2004 [58] 33 PAD patients admitted for elective PTA	VCAM-1, ICAM-1, P-sel, CRP	VCAM-1, ICAM-1 and hsCRP were all higher and P-sel significantly lower in patients with systemic arterial disease. P-Selectin, VCAM-1, hsCRP were elevated significantly for at least 2 weeks post PTA/stenting	A, B

<p>Tseng et al. 2004[120]</p> <p>557 patients with type II diabetes</p>	<p>Lp(a)</p>	<p>ABPI was associated with log [Lp(a)] especially in men or in patients with PAD.. Lp(a) levels increased from no PAD to mild and severe PAD.</p>	<p>B</p>
<p>Parsson et al. 2004[162]</p> <p>40 patients with CLI undergoing either femoro-popliteal or femoro-distal reconstruction</p>	<p>tPA, PAI-1, d-dimer, IL-6, IL-2 rec, MCP-1, IL-10, TAT</p>	<p>Patients with CLI had increased IL-6, IL-2 receptor, TAT, tPA, D-dimer and fibrinogen prior to revascularisation. Elevated tPA and D-dimer were found after 30 days posoperatively. Increased IL-6, IL-10, MCP-1 was observed after reperfusion but normalised after 30 days.</p>	<p>B</p>
<p>Riba et al. 2004[127]</p> <p>39 patients with IC 14 controls</p>	<p>Hcy</p>	<p>63% of patients with PAD were found to be mildly hyperhomocysteinaemic. Claudicants with elevated homocysteine had altered platelet function compared to controls</p>	<p>B</p>
<p>Koscielney et al. 2004[163]</p> <p>2821 men and women</p>	<p>Hct, plasma viscosity, fibrinogen, erythrocyte aggregation</p>	<p>In males with PAD, Hct, plasma viscosity, fibrinogen and erythrocyte aggregation were significantly higher than controls.</p>	<p>B, C</p>