

## Haemostatic and Inflammatory Markers in the Prediction of Cardiovascular Disease

a report by

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Clinicians and pathologists have long recognised the role of the haemostatic system in acute coronary and cerebral thrombosis, and anti-platelet, anticoagulant and fibrinolytic therapies are well established in clinical practice. Pathologists have suggested for several decades that 'hypercoagulability' contributes to the development of atheroma,<sup>1</sup> plaque formation and rupture.<sup>2,3</sup> Pioneering epidemiological studies suggested that markers of haemostasis as well as inflammation, such as fibrinogen,<sup>4,5</sup> white-cell count,<sup>6</sup> viscosity<sup>7</sup> and C-reactive protein (CRP)<sup>8</sup> are associated with risk of cardiovascular disease (CVD), and may have a role in both pathogenesis, and in long-term risk prediction. Low-grade inflammation is present in arterial plaques and may play a role in plaque rupture.<sup>8</sup>

The risk of a cardiovascular event has also been linked to the 'acute-phase response', the acute inflammatory and immunological response to infection. In a large case-series, based in a national primary care database, a first myocardial infarction (MI) and stroke were each more common following recent respiratory or urinary tract infections (UTIs), (relative risks (RRs) 5.0 and 3.2 for MI and stroke, respectively). The risk was greatest within the first three days after diagnosis and fell during the following weeks.<sup>9</sup> Hence, the roles of both acute, high-grade; and chronic, low-grade inflammation in the pathogenesis of CVD (which may be reduced by preventive or therapeutic interventions), and the evaluation of suitable haemostatic and inflammatory biomarkers, are growing research topics. *Table 1* summarises meta-analyses of individual risk markers that have been examined in prospective epidemiological studies to date.<sup>10-17</sup>

*Table 1* shows the odds of a coronary heart disease (CHD) event in a person with a value for each risk marker in the upper third of the population distribution compared with that of someone with a value in the lower third of the distribution. However, adjustment for classical risk factors and other confounders varies from publication to publication, and direct comparisons between the

size of the association (odds ratio) cannot be made reliably between these studies.

### Haemostatic Markers

Fibrinogen is the most studied haemostatic marker. A recent meta-analysis of individual participant data<sup>10</sup> observed strong associations with risk of CHD, stroke and other cardiovascular death. However, large-scale studies of functional genetic variants that affect fibrinogen levels, suggest that these associations may not be directly causal.<sup>18</sup> Furthermore, fibrinogen is also associated with risk of non-cardiovascular death, which suggests that its association with CVD is not specific.<sup>10</sup>

Fibrin D-dimer appears a clinically useful marker of coagulation activation. D-dimer assay is already widely used in clinical practice to rule out clinically suspected deep venous thrombosis and pulmonary embolism, since normal levels have a high negative predictive value for these conditions.<sup>19</sup> Clinical and epidemiological studies have linked D-dimer levels with atrial fibrillation and the risk of CHD or stroke,<sup>14,20-22</sup> and it has been suggested that D-dimer levels might be used in clinical practice to evaluate the need for oral anticoagulants in patients with atrial fibrillation.<sup>22</sup> Two common genetic thrombophilias (the factor V Leiden and prothrombin G20120A mutations), which are associated with increased coagulation activation and with increased risk of venous thromboembolism (RR 2-4),<sup>23</sup> have recently also been associated with risk of CHD (RR 1.2-1.4).<sup>17</sup>

A marker of fibrinolysis, tissue plasminogen activator, (t-PA) shows modest associations with risk of CHD, although the association is attenuated when adjustment is made for classical risk factors, e.g. lipids.<sup>13</sup> Associations between von Willebrand factor (vWF) and CHD are also modest.<sup>11</sup>

The evidence that functional polymorphisms for t-PA, vWF, coagulation factor VII, or plasminogen activator inhibitor type-1 (PAI-1) either promote or reduce hypercoagulability is inconclusive.<sup>17,23</sup>

**Table 1: Haemostatic/inflammatory Markers and Risk of Coronary Heart Disease: Summary of Meta-analyses for Individual Markers in Generally Healthy Cohort<sup>23</sup>**

Variable	CHD Cases (n)	Odds ratio (top third compared with bottom third of the population distribution) (95%CI)
<b>Phenotype</b>		
Fibrinogen <sup>10</sup>	7,213	1.8 (1.6–2.0)
C-reactive protein <sup>11</sup>	7,068	1.49 (1.37–1.62)
White cell count <sup>12</sup>	7,229	1.4 (1.3–1.5)
ESR <sup>12</sup>	4,386	1.33 (1.22–1.44)
Albumin <sup>12</sup>	3,770	1.5 (1.3–1.7) <sup>a</sup>
von Willebrand Factor <sup>11</sup>	3,969	1.23 (1.14–1.33)
Tissue plasminogen activator antigen <sup>13</sup>	2,119	1.47 (1.19–1.81)
D-dimer <sup>14</sup>	1,535	1.7 (1.3–2.2)
Plasma viscosity <sup>15</sup>	1,278	1.57 (1.34–1.85)
Haematocrit <sup>15</sup>	8,020	1.16 (1.05–1.29)
Plasminogen activator inhibitor type-1 <sup>13</sup>	833	0.98 (0.53–1.81)
Homocysteine <sup>16</sup>	5,073	0.89 (0.83–0.96) <sup>b</sup>
<b>Genotype (polymorphism)</b>		
Prothrombin 20120A <sup>17</sup>	11,625	1.31 (1.12–1.52)
V Leiden <sup>17</sup>	15,704	1.17 (1.08–1.28)
PAI-1 [-625]4G <sup>17</sup>	11,763	1.06 (1.02–1.10) <sup>c</sup>

CI=confidence intervals; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; VWF=von Willebrand factor; t-PA=tissue plasminogen activator; PAI=plasminogen activator inhibitor. a=For albumin, bottom third to top third; b=For homocysteine, 25% lower usual level; c=Publication bias probable.

Rare genetic variants of homocysteine are closely associated with premature thrombotic disorders, and homocysteine has been reported as a possible modest independent risk factor for cardiovascular risk.<sup>16</sup> A strong synergistic association between homocysteine and smoking habit has been reported.<sup>24</sup>

### Inflammatory Markers

Numerous markers of either acute or chronic inflammation can be detected in blood. Haematological inflammatory markers that have been linked to the risk of CHD include white-cell count, erythrocyte sedimentation rate (ESR) and plasma viscosity: these are also correlated with each other and also with fibrinogen.<sup>25</sup> Biochemical products of inflammation, such as CRP and low albumin, are produced as a result of the activity of pro-inflammatory cytokines, such as interleukin-6 and interleukin-18, which have each been linked with risk of CHD.<sup>26,27</sup> Again, these markers are correlated with each other and with haematological markers of inflammation, and also with other unmeasured factors; hence the process of establishing primary causality for individual markers requires further basic scientific research.

### Can Haemostatic/inflammatory Markers Improve Cardiovascular Risk Prediction in Clinical Practice?

Several well-established epidemiological studies

have reported that the addition of haemostatic or inflammatory markers can improve risk prediction of CVD.<sup>28–30</sup> Particular interest has focussed on CRP,<sup>11</sup> but a range of markers has been proposed from other studies.<sup>29,30</sup>

A recent report in the US proposed that CRP should be an 'option' in predicting CHD risk,<sup>31</sup> but this proposal has been questioned both in the US<sup>32–35</sup> and in Europe.<sup>23,36</sup>

Incorporation of CRP and other emerging risk factors into routine practice for prediction of cardiovascular risk may be premature, therefore, and criteria for the rigorous evaluation of such factors have been proposed.<sup>37</sup> These criteria include: applicability to all relevant clinical cardiovascular events; ability to predict in short-, intermediate- and long-term follow-up; standardised measurements; examination of variability; the degree of correlation with established risk factors; and improvement in overall prediction, among other criteria.

Current investigation of determinants of inflammatory markers, which include physical activity,<sup>38</sup> dietary factors,<sup>39</sup> alcohol<sup>40</sup> and weight-loss<sup>41</sup> as protective factors, and infections that promote periodontitis (a potentially treatable risk factor),<sup>42</sup> encourage the detailed examination of these biomarkers in future research. ■

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