AF - endothelial changes/
inflammation/
hypercoagulability

GREGORY Y H LIP
MD FRCP (Lond Edin Glasg)  FACC FESC
Professor of Cardiovascular Medicine, University of
Birmingham, UK
Adjunct Professor of Cardiovascular Sciences, Thrombosis
Research Unit, Aalborg University, Denmark
Visiting Professor of Cardiology, University of Belgrade, Serbia

Centre for Cardiovascular Sciences
City Hospital
Birmingham  B18  7QH
England UK

Consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer,
Biotronik, Medtronic, Portola, Boehringer Ingelheim,
Microlife and Daiichi-Sankyo.
Speakers bureau for Bayer, BMS/Pfizer, Medtronic,
Boehringer Ingelheim, Microlife and Daiichi-Sankyo
Virchow’s triad and AF......

*Lip Lancet 1995; 346: 1313-14*

abnormalities of vessel wall
(endothelial dysfunction or damage)

abnormalities of blood flow
(rheology, viscosity and flow reserve)

abnormalities of blood constituents
(abnormal haemostatic factors, platelet activation and fibrinolysis)

……..AF confers a prothrombotic or hypercoagulable state.
Components of Virchow’s triad for thrombogenesis in AF

Abnormal changes shown in the vessel wall (e.g., atrial tissue changes, endothelial damage and dysfunction), in flow (stasis—e.g., in the left atrial appendage), and in blood constituents (e.g., haemo-concentration, platelets, coagulation cascade activation, inflammation); all factors contribute to propensity for thrombus formation (thrombogenesis).
‘Structural’ and ‘Flow’ abnormalities leading to thrombogenesis in AF

Severely damaged left atrial appendage endocardial surface with thrombotic mass

Atrial endocardial changes in mitral valve disease: a scanning electron microscopy study.


SEM appearance at magnification ×1600. Well-demarcated endothelial cells with perforations on cell surface clustered at intercellular junctions (type Iib or minimal changes).

SEM at magnification ×900. Severely damaged endocardial surface with thrombotic mass composed mainly of erythrocytes. Thrombotic mass appears incorporated onto endocardial surface (type IIIa).
‘Stasis’ within the left atrium in AF

...also, the association between AF and heart failure, dilated LA/LV, low LAA velocities etc

LAA flow during AF, as determined by pulsed Doppler during TEE
Accumulation of risk factors enhances the prothrombotic state in AF

Ohara et al

Int J Cardiol 2008; 126:316–321

Effect of risk level on hemostatic markers

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>Nonvalvular AF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin group</td>
<td>Non-warfarin group</td>
</tr>
<tr>
<td>0</td>
<td>66 (21.8)</td>
<td>95 (32.9)</td>
</tr>
<tr>
<td>1</td>
<td>87 (28.8)</td>
<td>94 (32.5)</td>
</tr>
<tr>
<td>2</td>
<td>72 (23.8)</td>
<td>54 (18.7)</td>
</tr>
<tr>
<td>3</td>
<td>44 (14.6)</td>
<td>33 (11.4)</td>
</tr>
<tr>
<td>4</td>
<td>21 (7.0)</td>
<td>11 (3.8)</td>
</tr>
<tr>
<td>5</td>
<td>12 (4.0)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are number of patients (%). AF = atrial fibrillation.

<table>
<thead>
<tr>
<th>Thromboembolic risk level</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin group</td>
<td>75.5±56.5</td>
<td>104.4±91.3*</td>
<td>136.0±155.8*</td>
</tr>
<tr>
<td>Non-warfarin group</td>
<td>88.0±61.0</td>
<td>149.2±115.8*</td>
<td>175.4±144.0*</td>
</tr>
<tr>
<td>Control</td>
<td>41.8±41.7</td>
<td>77.1±96.6</td>
<td>75.3±87.1</td>
</tr>
<tr>
<td>F1+2 (nmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin group</td>
<td>0.40±0.24</td>
<td>0.52±0.42</td>
<td>0.54±0.49</td>
</tr>
<tr>
<td>Non-warfarin group</td>
<td>0.81±0.54</td>
<td>0.97±0.53*</td>
<td>1.00±0.65*</td>
</tr>
<tr>
<td>Control</td>
<td>0.82±0.33</td>
<td>0.99±0.34*</td>
<td>0.90±0.46</td>
</tr>
</tbody>
</table>

Values are mean±SD. F1+2 = prothrombin fragment F1+2.

* p<0.05 vs low thromboembolic risk level.

Levels of markers of platelet activation (platelet factor 4 and \( \beta \)-thromboglobulin) were increased in NVAF patients but not affected by the risk level.
The Oral Direct Thrombin Inhibitor AZD0837 for the Prevention of Stroke and Systemic Embolism in AF: A Phase II Randomized Dose Guiding, Safety and Tolerability Study


Figure 1. Trial design

Figure 2. D-dimer levels in (a) VKA-naïve patients and (b) VKA-pre-treated patients (full analysis set)
Phase 2 study comparing edoxaban, with warfarin for stroke prevention in patients with AF

Weitz et al
Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial

Mega et al Lancet 2015 ttp://dx.doi.org/10.1016/S0140-6736(14)61994-2

Figure 3: Overt bleeding events in the first 90 days of treatment among patients taking warfarin, across genotype bins and HAS-BLED bleeding risk score
Global p<0.0001.

Cumulative incidence of overt bleeding events in the first 90 days of treatment among patients taking warfarin, across genotype bins.
D-dimer level influences thromboembolic events in AF  
Nozawa et al Int J Cardiol 2006;109:59 – 65

Solid lines show patients with the level of the coagulative marker below the upper limit of the normal range.

Dotted lines show patients with the level of the coagulative marker exceeding the upper limit of the normal range.
Relationship Between Plasma vWF and Cardiovascular Outcome in AF: *Kaplan-Meier Survival Analysis*

994 (mean age 69yrs; 25%F) receiving aspirin in the SPAF III
### Additive Role of Plasma vWF Levels to Clinical Factors for Risk Stratification in AF

*Lip et al Stroke 2006;37:2294-2300*

<table>
<thead>
<tr>
<th>Risk Score Level</th>
<th>Annualized Rate (95% CI)</th>
<th>vWF Level</th>
<th>Annualized Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birm, low</td>
<td>0 (0–0)</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Birm, moderate</td>
<td>1.95 (1.17–2.92)</td>
<td>Low</td>
<td>1.44 (0.69–2.48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>3.18 (1.44–5.59)</td>
</tr>
<tr>
<td>Birm, high</td>
<td>5.75 (3.68–8.28)</td>
<td>Low</td>
<td>4.88 (2.51–8.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>6.98 (3.59–11.5)</td>
</tr>
<tr>
<td><strong>CHAD, low</strong></td>
<td>0.65 (0.12–1.60)</td>
<td>Low</td>
<td>0.54 (0.05–1.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>1.09 (0.00–4.27)</td>
</tr>
<tr>
<td><strong>CHADS, moderate</strong></td>
<td>2.72 (1.76–3.89)</td>
<td>Low</td>
<td>2.24 (1.22–3.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>3.73 (1.85–6.26)</td>
</tr>
<tr>
<td><strong>CHADS, high</strong></td>
<td>7.03 (3.92–11.0)</td>
<td>Low</td>
<td>5.68 (2.04–11.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>8.37 (3.79–14.7)</td>
</tr>
</tbody>
</table>

Annualized Stroke Event Rates for Birmingham (Birm) and CHADS2 Risk Scores by vWF Level...
Biomarkers in atrial fibrillation: a clinical review

Hijazi et al
Eur Heart J 2012

Various biomarkers have been used to aid risk stratification in AF ..

- D-dimer, vWF, BNP, CRP, troponin, etc

Cumulative hazard rates for stroke or systemic embolism, according to Troponin I levels at randomization in RE-LY

Cumulative major adverse cardiovascular and cerebrovascular events (MACCE) free survival of patients with CX3CL1 levels $\leq 0.24$ ml (lower quartile) and patients with CX3CL1 $>0.24$ ng/ml.

Receiver operator characteristic analysis of CHADS$_2$ score and CHADS$_2$ plus CX3CL1 $>0.24$ ng/ml for the outcome of major adverse cardiovascular and cerebrovascular events (MACCE). C-index 0.60, 95% CI 0.51–0.67 vs. 0.67, 95% CI 0.58–0.75 respectively, $Z = 1.6$, $p = 0.1$. 
Growth Differentiation Factor 15, a Marker of Oxidative Stress and Inflammation, for Risk Assessment in Patients With AF


GDF-15 is a marker of oxidative stress and inflammation.
Growth Differentiation Factor 15, a Marker of Oxidative Stress and Inflammation, for Risk Assessment in Patients With AF


GDF-15 is a marker of oxidative stress and inflammation.

GDF-15 is a risk factor for major bleeding, mortality, and stroke in atrial fibrillation.

The prognostic value for major bleeding and death remained even in the presence of N-terminal pro-brain natriuretic peptide and high-sensitivity troponin I, in a selected trial cohort of anticoagulated AF patients.
The levels of vWF and IL6 – but not sP-sel – increased significantly 24h after procedure (p<0.001). Baseline vWF was significantly associated with persistent AF (p = 0.006 for peripheral and cardiac levels, respectively), while persistent AF (p = 0.031) and LAA flow pattern (p<0.001) remained associated with vWF in cardiac blood after ablation.

Advanced age was significantly associated with IL6 levels at baseline and after ablation in peripheral and cardiac blood.
‘….. the value of clinical risk scores would be enhanced by biomarkers that can include blood markers (e.g. vWF), urine (for example, proteinuria, eGFR or creatinine clearance), cardiac imaging (echocardiography, whether transthoracic or transoesophageal) and/or cerebral imaging (e.g. CT or MRI imaging) which can offer incremental predictive value for the identification of ‘high risk’ subjects.

……. this would be at the cost of reduced simplicity and practicality, limiting its (immediate) ‘quick’ use in everyday clinical practice’
Biomarkers that assess endothelial/inflammatory/hypercoagulability changes in AF offer the following:

- additional insights into pathophysiology
- potential surrogates for complications or risk.
- surrogate markers for testing antithrombotic regimes

For treatment decisions beyond identification of ‘low-risk’ patients (that can be successfully done with clinical risk scores such as CHA$_2$DS$_2$-VASc), additional efforts to identify high-risk patients by multiple biomarkers may not necessarily change management decisions, at least for thromboprophylaxis.

- The management decision (to use OAC or not) is already made after that initial first step to pick out the low-risk patients; making subsequent refinement of stroke risk in those with CHA$_2$DS$_2$-VASc score $\geq$ 2 (with biomarkers, single or multiple, old or new) matters much less.

New biomarkers are academically interesting but need to be proved useful (and practical) before adoption in influencing clinical decision making.
Levels of NT-proBNP are often elevated in AF and independently associated with an increased risk for stroke and mortality.

NT-proBNP improves risk stratification beyond the CHA₂DS₂-VASc score and might be a novel tool for improved stroke prediction in AF.