Celebrating 30 years of the MIDSPAN Studies

Haemostasis and thrombosis in the MIDSPAN study

Gordon Lowe
Inheritance of Hemophilia
Equal Chance with Each Pregnancy

XX
Carrier

XX
Carrier mother (XX)

xy
Hemophiliac

xy
LOW CLOTTING FACTORS INCREASE BLEEDING, BUT DECREASE THROMBOSIS  

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
<th>CHD risk</th>
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<tbody>
<tr>
<td>Normal</td>
<td>100%</td>
<td>1</td>
</tr>
<tr>
<td>Carrier female</td>
<td>50%</td>
<td>0.7</td>
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<tr>
<td>Haemophilia male</td>
<td>&lt;20%</td>
<td>0.2</td>
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(e.g. haemophilia (x-linked recessive))  

(Rosendaal et al 1991; Sramek et al 2003)
LOW COAGULATION INHIBITION (FACTOR V LEIDEN) AND THROMBOSIS

- Genetic cause (Bertina et al, 1994) of resistance to activated protein C (natural anticoagulant, Dahlback et al 1993); 3% of population (Lowe et al, 1999, 2001)
- Venous thrombosis 5.0 (Rosendaal et al, 1995)
- CHD 1.25 (Ye et al, 2005)
COAGULATION ACTIVATION (D-DIMER)

- Heritability 70% (Ariens et al, 2002; Banfield et al, 2005)
- Venous thrombosis 1.7 (Lowe et al, 1999; Prandoni et al, 2004)
- CHD 1.7 (Lowe et al, 1998)
Cumulative probability of recurrence

- D-Dimer > 500 ng/ml
- D-Dimer ≤ 500 ng/ml

Days
D-DIMER AND CHD

Thrombosis Prevention Trial showed that low dose Warfarin lowers risk of CHD, if lowers D-dimer (McCallum et al, 2004)
MIDSPAN AND HAEMOSTASIS

• Heritability
• CHD risk factors
• COC and HRT • 3 X DVT

• 1.5 x stroke, CHD
• mechanisms?
ORAL OESTROGENS AND COAGULATION

• ↑ factor IX
• ↓ antithrombin
• ↑ resistance to APC (like V Leiden)
• ↑ D-dimer
• ↑ CRP
• All associated with DVT, especially in HRT users (Lowe et al, 1999)
MIDSPAN STUDIES OF FEMALE HORMONES AND COAGULATION

- No effect of transdermal HRT, cf. oral HRT (Lowe et al, 2001)
- No effect of progesterone–only OCP, cf. COC (Rumley et al, 2003)
- Consistent with no DVT risk in epidemiological studies (Scarabin et al, 2003)
- Consider in women at increased thrombotic risk
CONCLUSIONS

• Haemostatic factors are associated with increased risk of arterial and venous thrombosis in epidemiological studies
• May be biological basis for associations
• May predict high risk groups for selection of therapies (e.g. oral contraceptives and HRT) or antithrombotic therapies