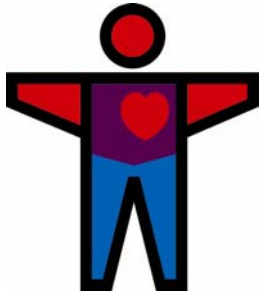
Celebrating 30 years of the MIDSPAN Studies



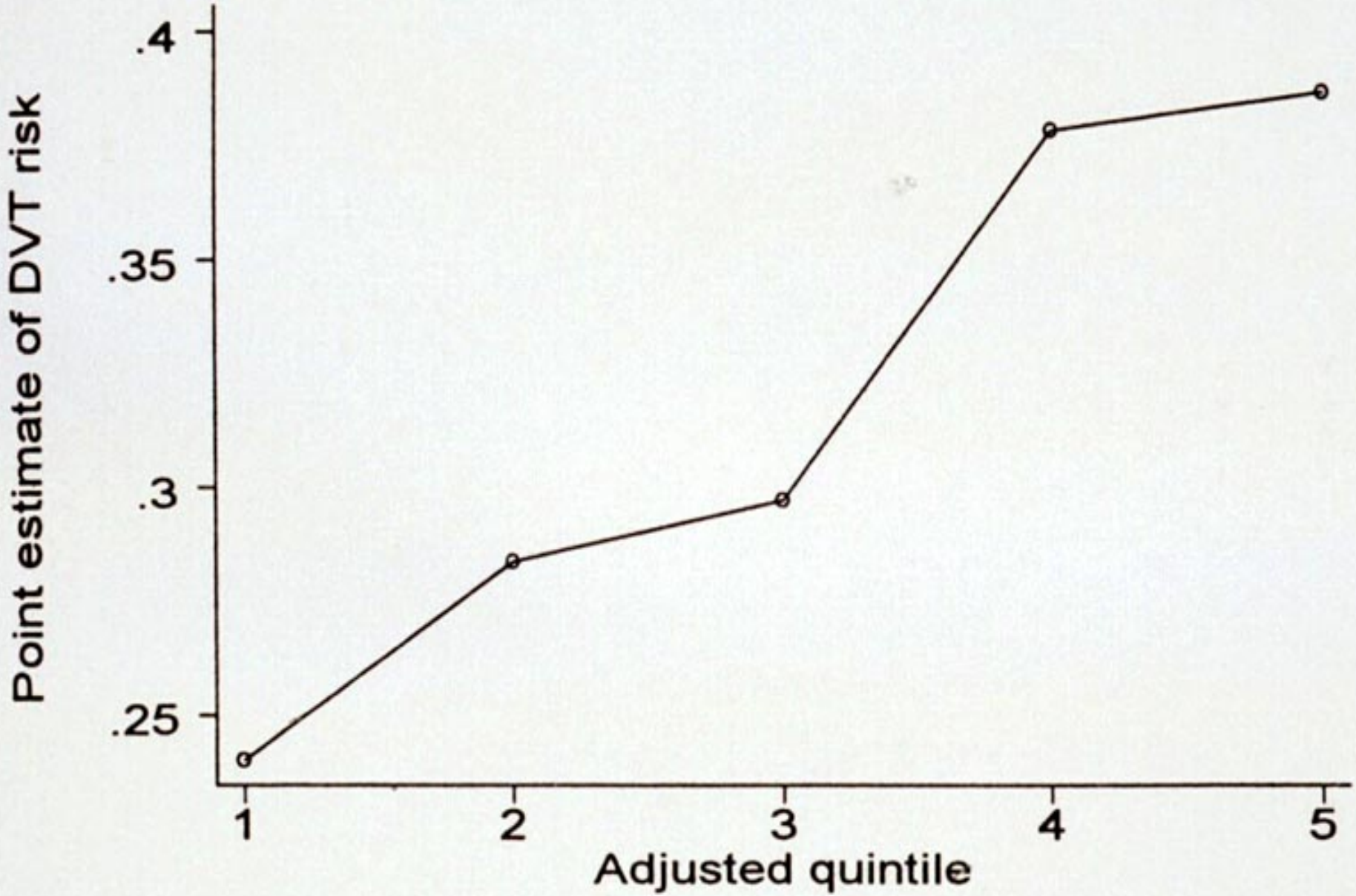
Haemostasis and thrombosis in the MIDSPAN study

Gordon Lowe


Inheritance of Hemophilia
Equal Chance with Each Pregnancy
?
XX
XX
Carrier
XY
Hemophiliac
XY
Carrier mother (XX)
X
Y
X
X

LOW CLOTTING FACTORS INCREASE BLEEDING, BUT DECREASE THROMBOSIS

e.g. haemophilia (x-linked recessive)		
	Level	CHD risk
Normal	100%	1
Carrier female	50%	0.7
Haemophilia male	<20%	0.2
(Rosendaal et al 1991; Sramek et al 2003)		



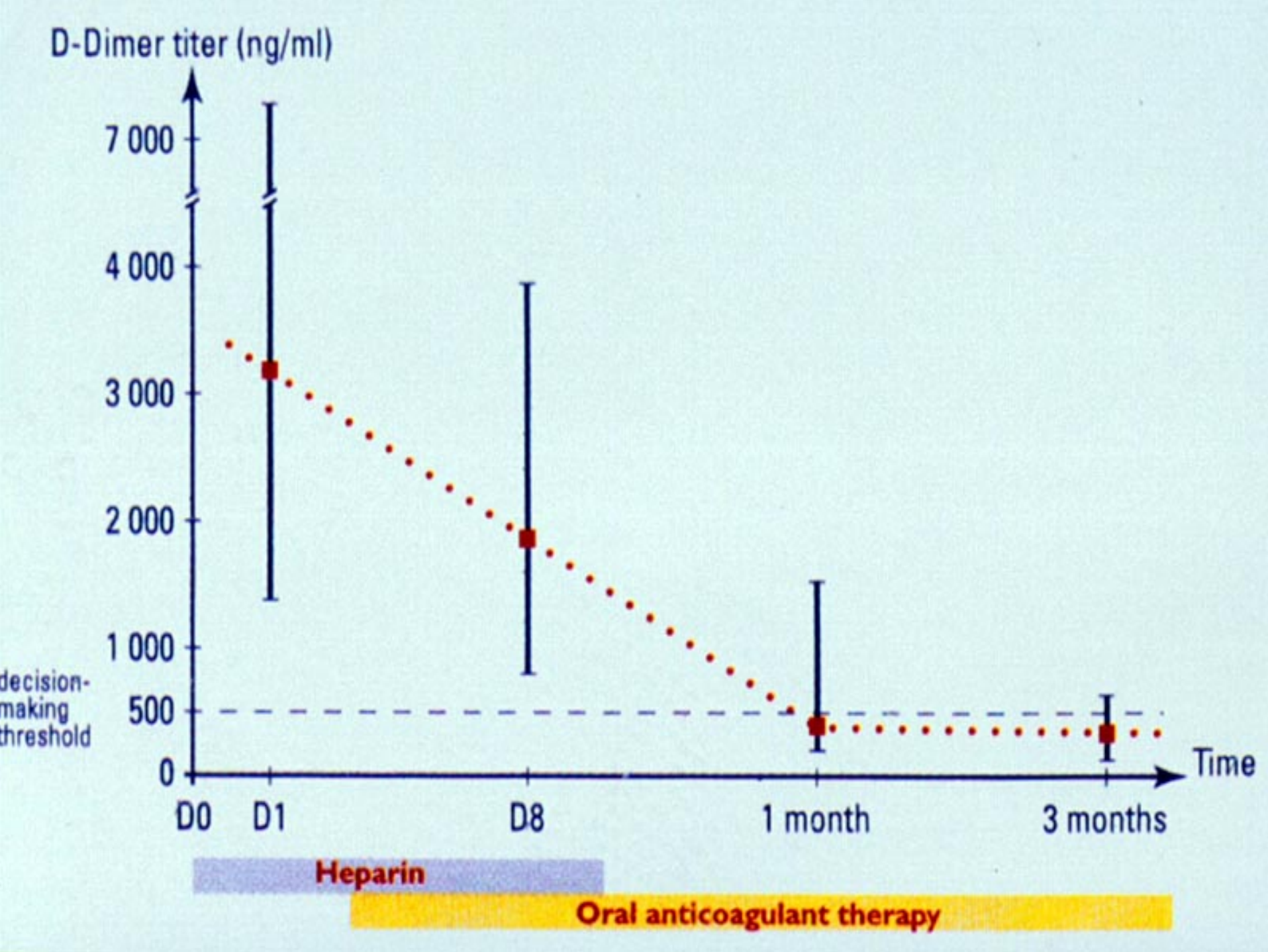
Factor VIIIc

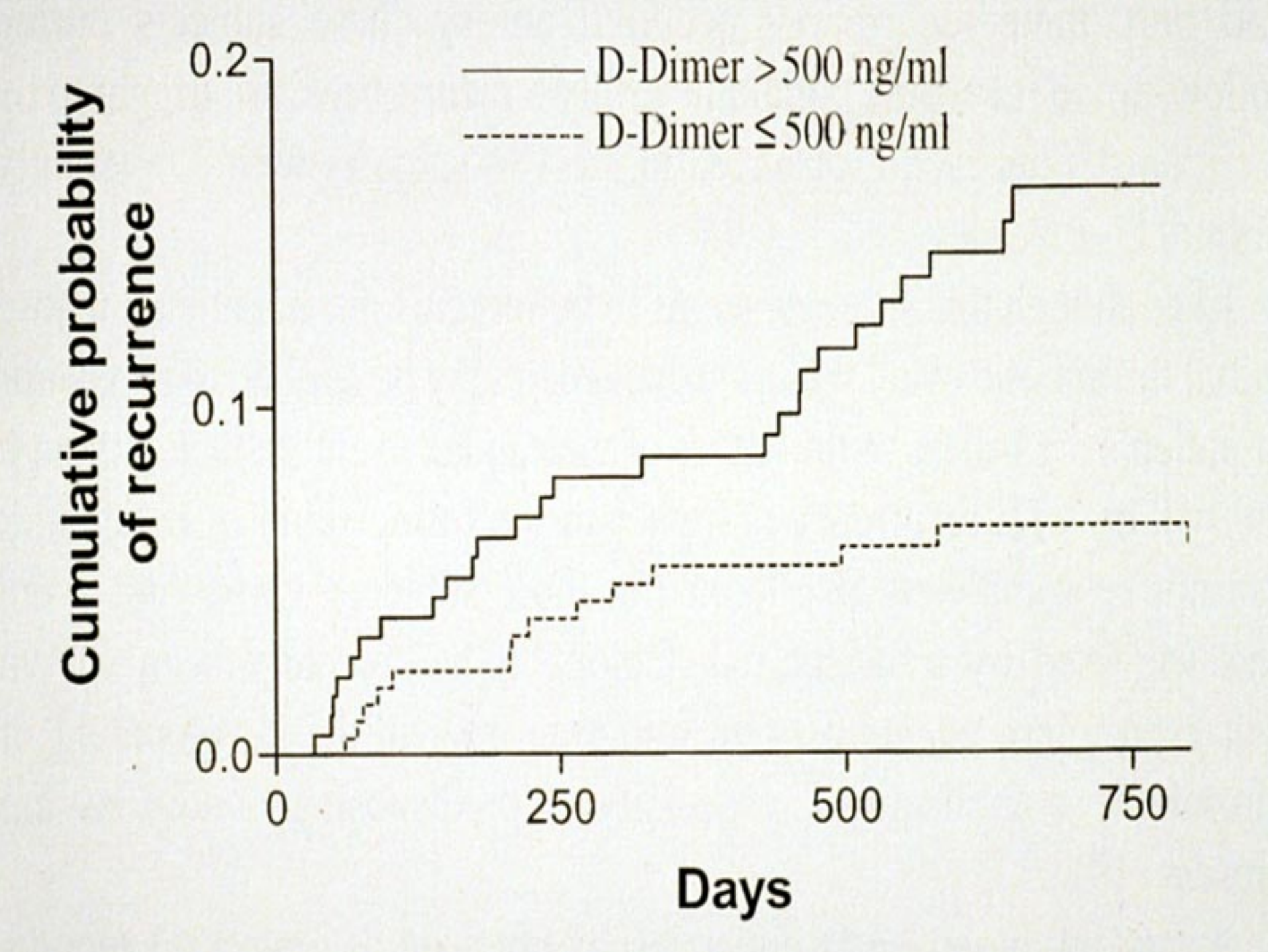
LOW COAGULATION INHIBITION (FACTOR V LEIDEN) AND THROMBOSIS

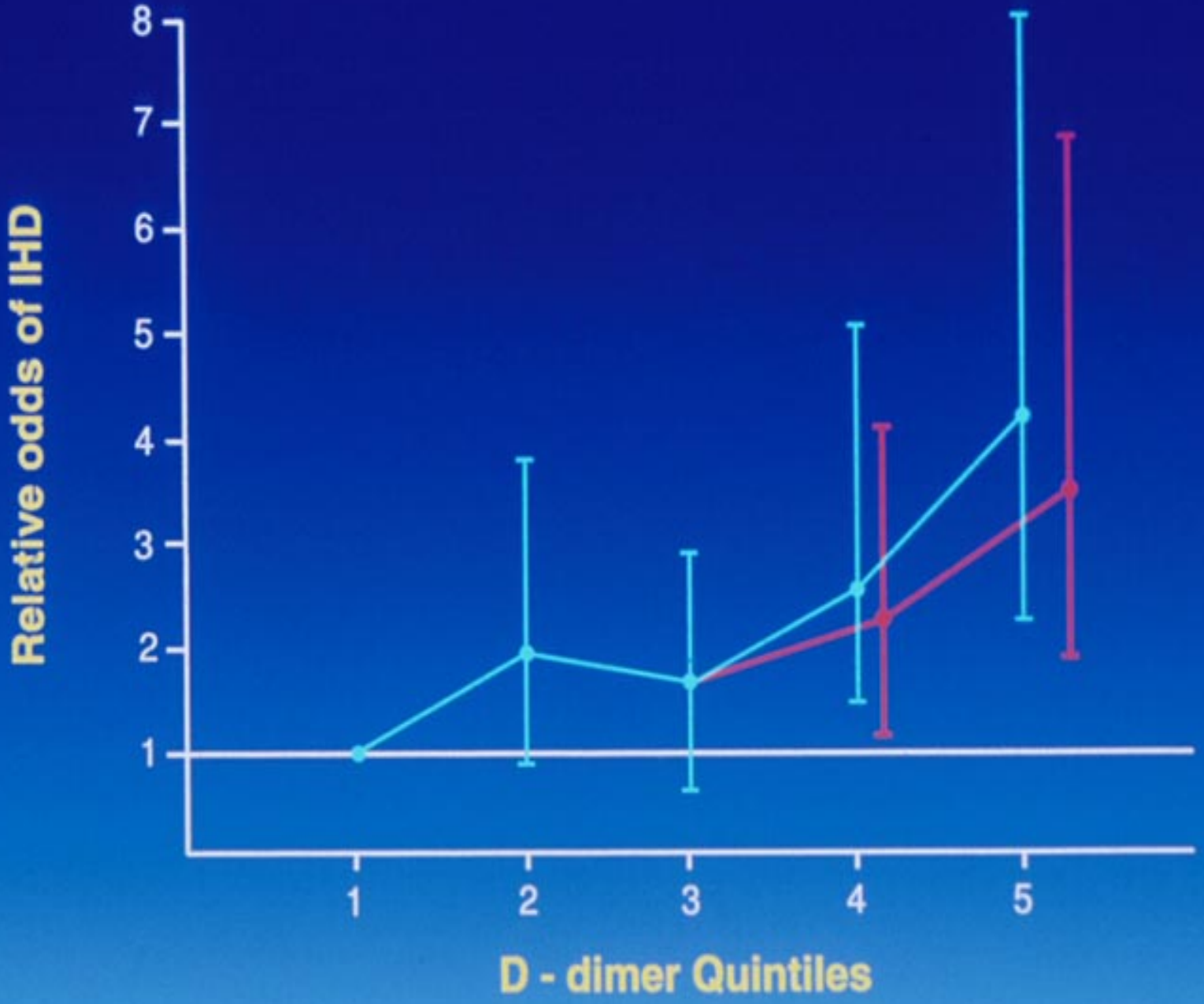
- Genetic cause (Bertina et al, 1994) of resistance to activated protein C (natural anticoagulant, Dahlback et al 1993); 3% of population (Lowe et al, 1999,2001)
- Venous thrombosis 5.0 (Rosendaal et al,1995)
- CHD 1.25 (Ye et al, 2005)

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)


D-Dimer titer (ng/ml)
7 000
4 000
3 000
2 000
1 000
500
0
decision-making threshold
Time
D0
D1
D8
1 month
3 months
Heparin
Oral anticoagulant therapy


D-Dimer >500 ng/ml
D-Dimer ≤500 ng/ml
Cumulative probability of recurrence
0.2
0.1
0.0
0
250
500
750
Days


Relative odds of IHD
8
7
6
5
4
3
2
1
1
2
3
4
5
D - dimer Quintiles

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