EQAS indications for opportunities for improvement?

On behalf of the EQALM
Piet Meijer
ECAT Foundation
The Netherlands

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SCOPE

EQALM, European Organisation for External Quality Assurance Providers in Laboratory Medicine, provides a forum for co-operation and exchange of knowledge on quality-related matters especially with regard to external quality assessment / assurance programmes in Europe.

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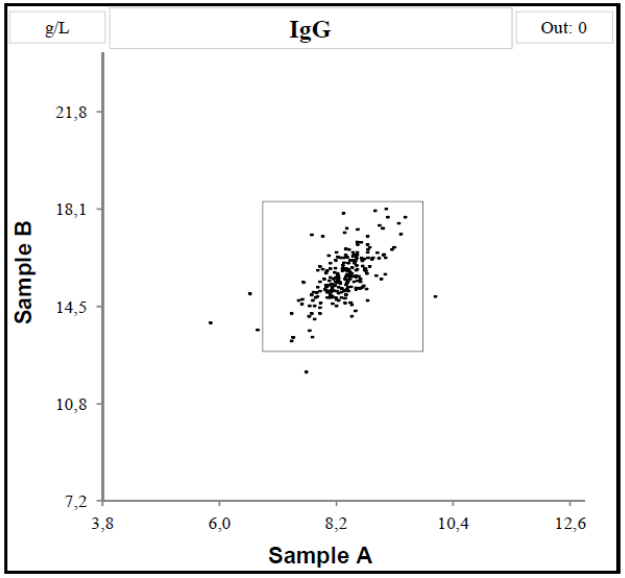
Examples from EQA programmes

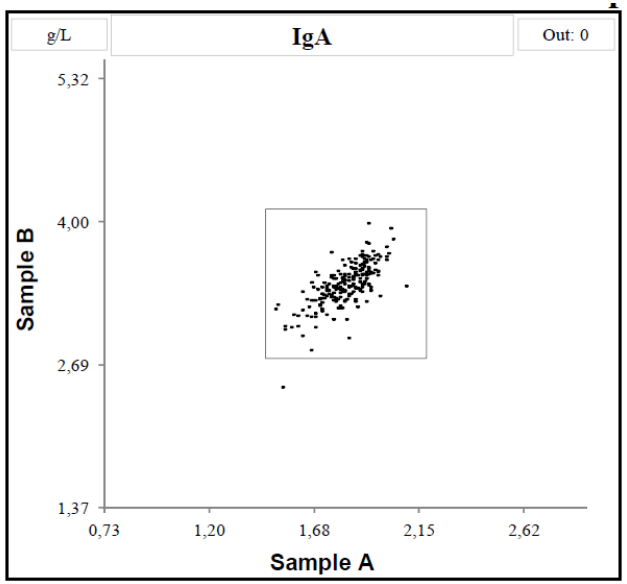
IgG / IgA

Consensus Value

IgG (g/L)	N	RoM	SD	CV (%)
Sample A	219	8.35	0.40	4.7
Sample B	219	15.6	0.81	5.2

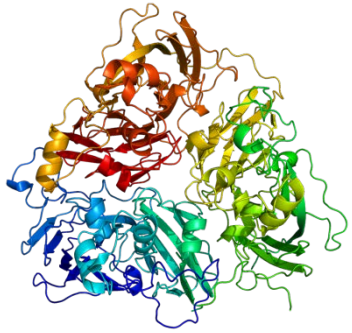
IgA (g/L)	N	RoM	SD	CV (%)
Sample A	220	1.82	0.10	5.6
Sample B	220	3.43	0.18	5.1





SEKK – Czech Repl.

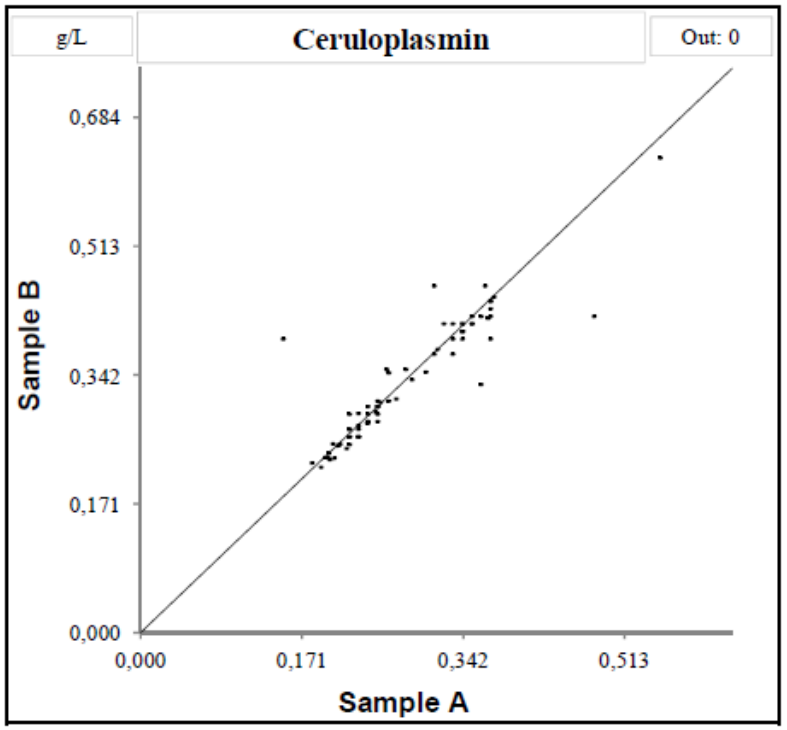
Ceruloplasmin (g/L)



Consensus Value

Sample A	N	RoM	SD	CV (%)
All	72	0.230	0.030	13
Roche (IT)	16	0.223	0.015	6.7
Siemens (IN)	11	0.212	0.008	11
Beckman (IT)	8	0.194	0.009	5.0
Beckman (IN)	13	0.249	0.019	7.4

Sample A	N	RoM	SD	CV (%)
All	72	0.438	0.065	15
Roche (IT)	16	0.429	0.026	6.2
Siemens (IN)	11	0.399	0.033	8.2
Beckman (IT)	8	0.365	0.022	6.1
Beckman (IN)	13	0.512	0.036	7.0



IN = Immunonephelometry
IT = Immunoturbidimetry

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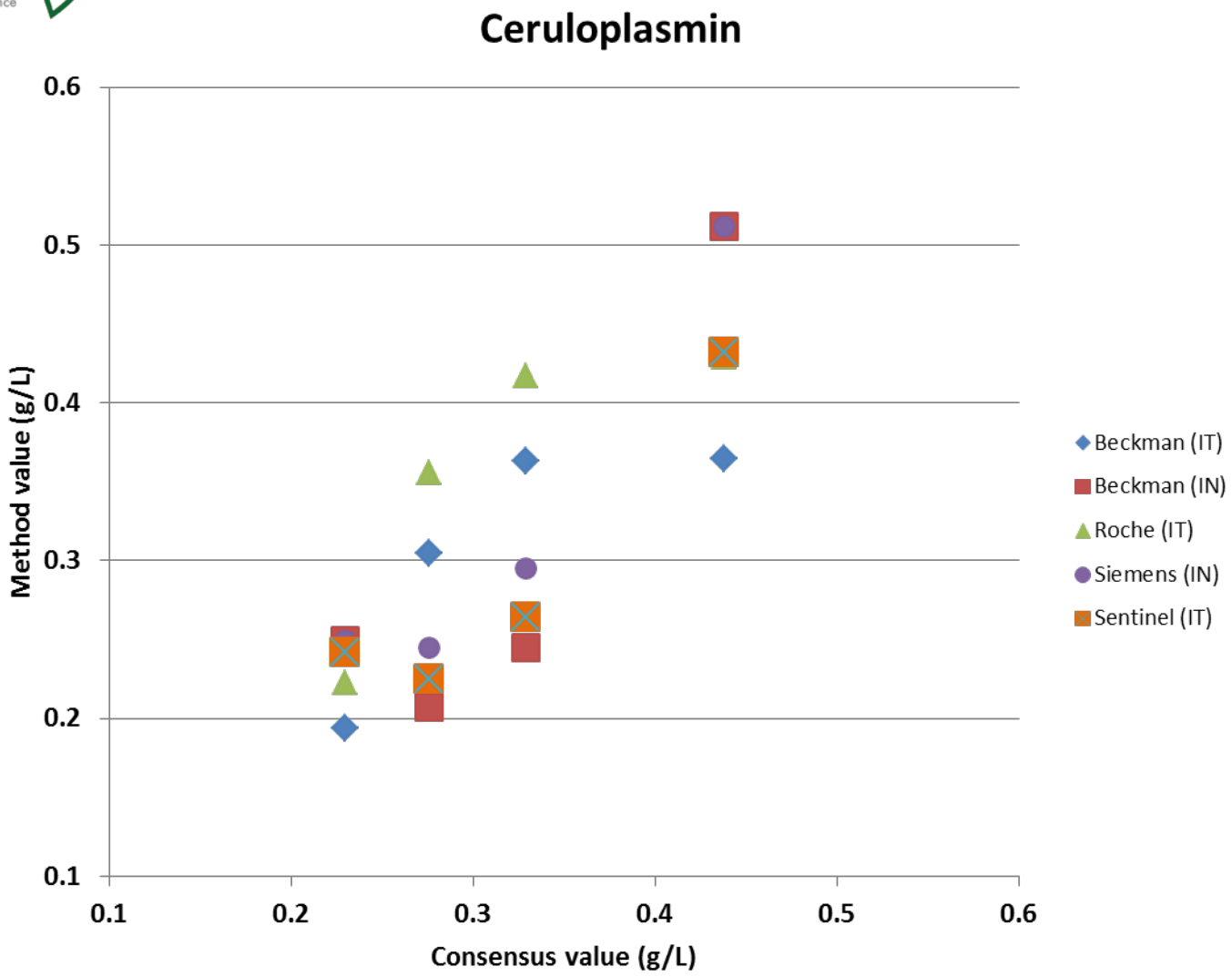
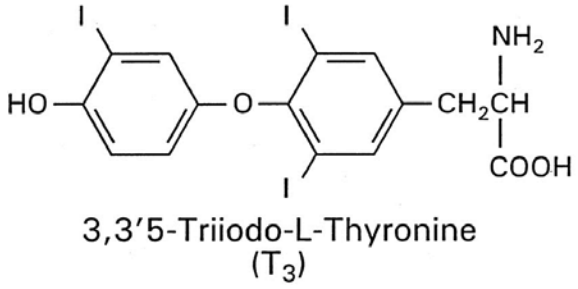


SEKK – Czech Repl.

Total T3 (nmol/L)

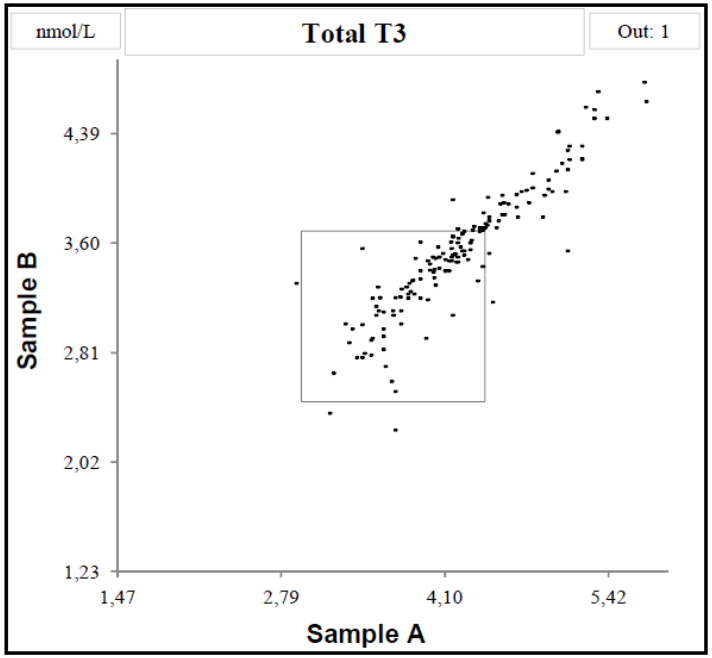


3,3'5-Triiodo-L-Thyronine
(T_3)

Assigned Value

All	N	Cert. RV	RoM	Bias (%)
Sample A	159	3.69	4.21	14
Sample B	159	3.08	3.54	15

Sample A	N	Cert. RV	RoM	Bias (%)
All	159	3.69	4.21	14
Abbott	24		3.79	2.7
Beckman	9		3.53	-4.4
Roche	60		4.25	15
Siemens – DPC	15		3.67	-0.5
Siemens – Bayer	39		4.90	33



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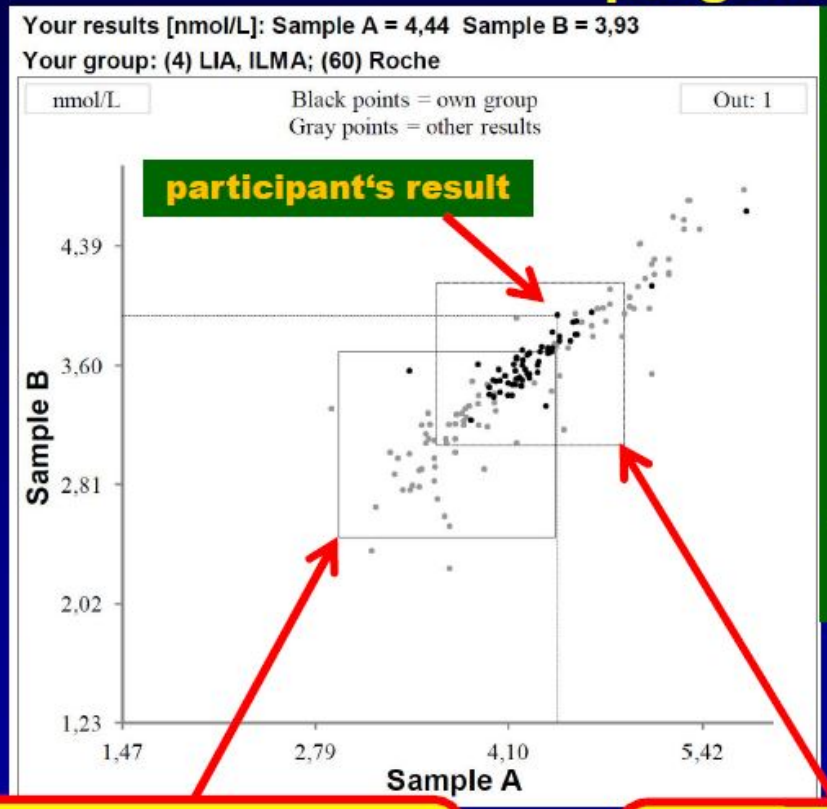
Total T3 (nmol/L)

Using two different D_{max} values in endocrinology programs



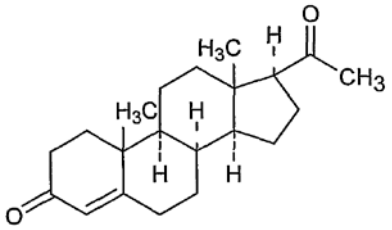
Comment

- **Analyte T3 total**
- The bias of Roche group is clearly visible.
- Participant's result evaluation: it is not traceable, but it is comparable to the results of its own group (Roche)
- **Conclusion: participant succeeded**

traceability criterion: AV (CRV) ± 20 %

comparability criterion: AV (group mean) ± 15 %

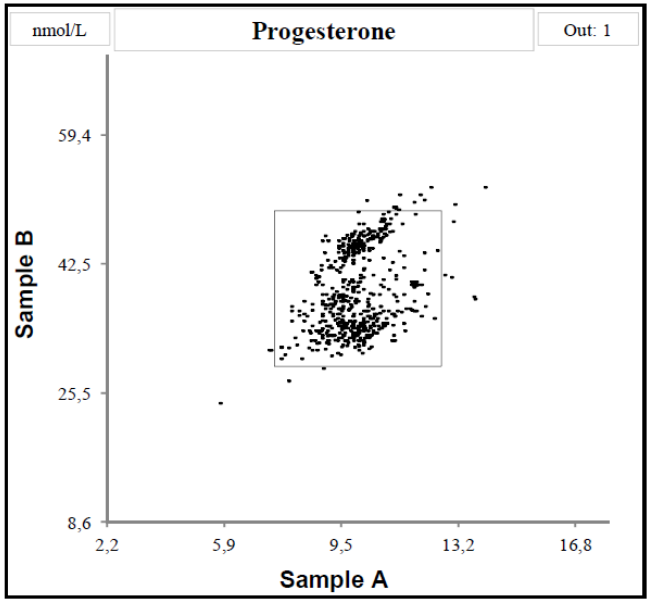
Progesterone (nmol/L)



Assigned Value

All	N	CRV	RoM	Bias (%)
Sample A	581	10.03	10.0	-0.31
Sample B	581	39.22	38.9	-0.94

Sample B	N	RoM A	Bias (%)	RoM B	Bias (%)
All	581	10.0	-0.31	38.9	-.094
DRG	41	11.5	15	39.9	1.8
Abbott	75	9.47	-5.3	38.1	-2.8
Beckman	39	9.05	-9.8	35.2	-10.2
Roche	178	10.1	0.1	45.3	15.6
Siemens – DPC	137	10.3	3.0	34.2	-12.8
Siemens – Bayer	95	9.57	-4.6	34.6	-11.7



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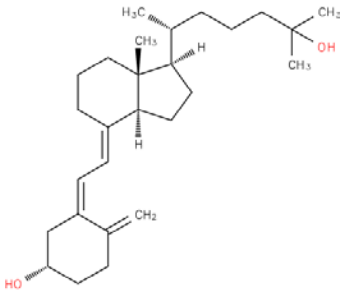
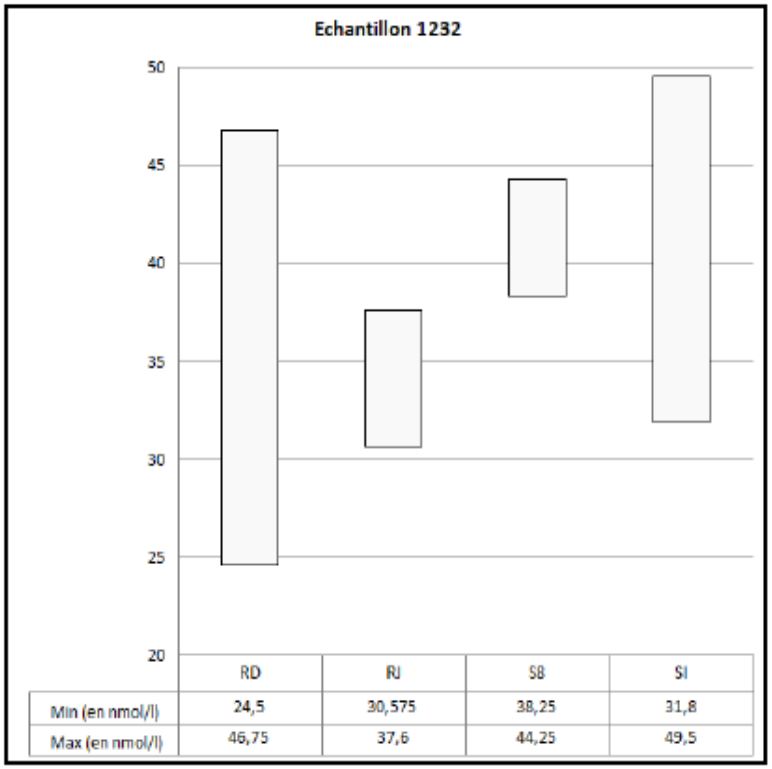
Calcidiol (25-hydroxyvitamin D)



The plasma level of calcidiol is the biological marker for assessing the status of vitamin D. In children, a deficiency threshold (higher risk of poor bone mineralization or extra bone pathology) was set at 50 nmol/L and a waiting threshold (high risk of rickets) to 30 nmol/L.

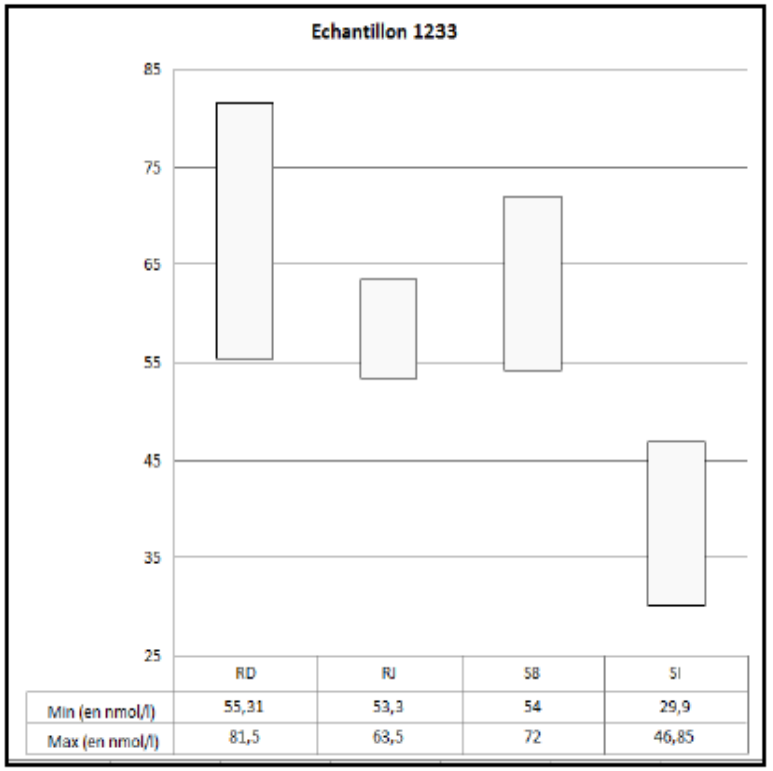
Calcidiol (25-hydroxyvitamin D)

Lyophilised



	RD	RJ	SB	SI
Min (en nmol/l)	24,5	30,575	38,25	31,8
Max (en nmol/l)	46,75	37,6	44,25	49,5

Fresh

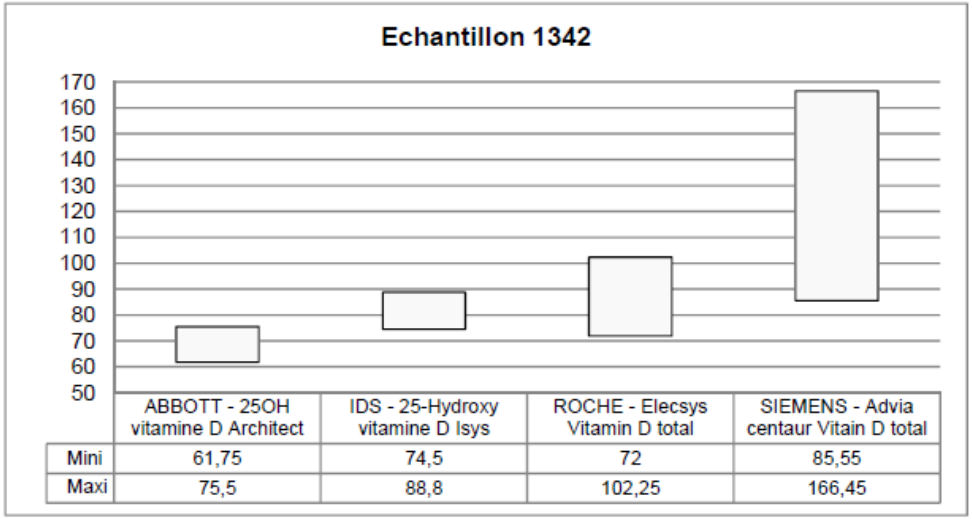


	RD	RJ	SB	SI
Min (en nmol/l)	55,31	53,3	54	29,9
Max (en nmol/l)	81,5	63,5	72	46,85

CTCB - France

Calcidiol (25-hydroxyvitamin D)

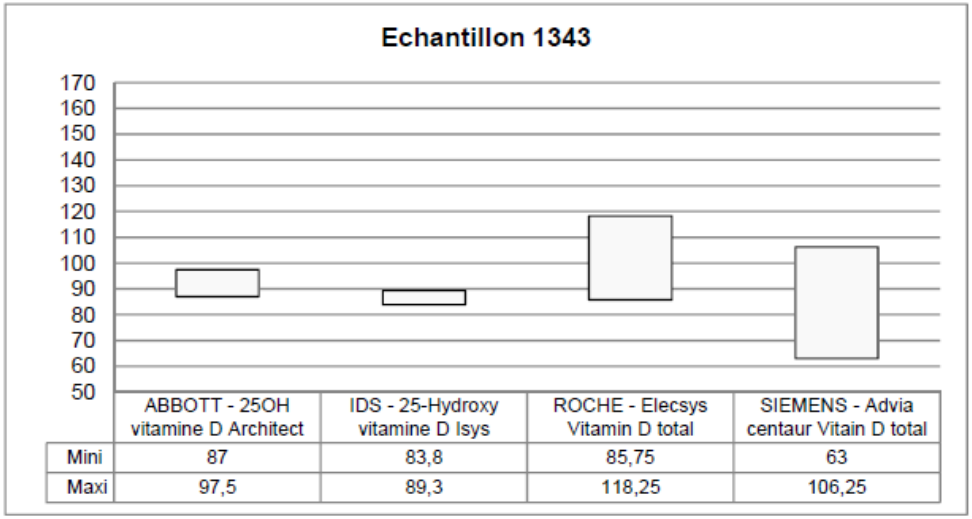
Lyophilised



	ABBOTT - 25OH vitamine D Architect	IDS - 25-Hydroxy vitamine D Isys	ROCHE - Elecsys Vitamin D total	SIEMENS - Advia centaur Vitain D total
Mini	61,75	74,5	72	85,55
Maxi	75,5	88,8	102,25	166,45

Graphique 2 - Echantillon 1342 - en nmol/L : Répartition des résultats par réactif après troncature des valeurs aberrantes

Fresh



	ABBOTT - 25OH vitamine D Architect	IDS - 25-Hydroxy vitamine D Isys	ROCHE - Elecsys Vitamin D total	SIEMENS - Advia centaur Vitain D total
Mini	87	83,8	85,75	63
Maxi	97,5	89,3	118,25	106,25

Graphique 3 - Echantillon 1343 - en nmol/L : Répartition des résultats par réactif après troncature des valeurs aberrantes

CTCB - France

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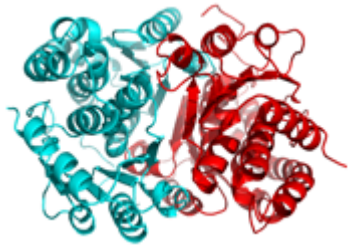
D-Dimer



D-dimer (or D dimer) is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two crosslinked D fragments of the fibrin protein. D-dimer concentration may be determined by a blood test to help diagnose thrombosis. Since its introduction in the 1990s, it has become an important test performed in patients with suspected thrombotic disorders. While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential causes. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. In addition, it is used in the diagnosis of the blood disorder disseminated intravascular coagulation

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D-Dimer

ECAT Programme

	N	Value	CV (%)	Value	CV (%)
DD units (mg/L)					
I.L. HemosIL D-Dimer HS	44	0.23	7.2	0.29	7.1
Medirox D-Dimer	49	0.17	15.9	0.22	12.2
FEU units (mg/L)					
BioMerieux Vidas	34	0.69	4.1	1.17	3.7
I.L. HemosIL D-Dimer HS500	51	0.75	7.5	0.94	7.0
Roche Tinaquant 2nd gen. (cal. citrate)	45	0.50	18.6	0.68	11.9
Siemens Innovance D-Dimer	209	0.71	7.3	1.03	8.3
Stago / Roche Liatest D-Dimer	122	0.68	9.8	1.09	9.3

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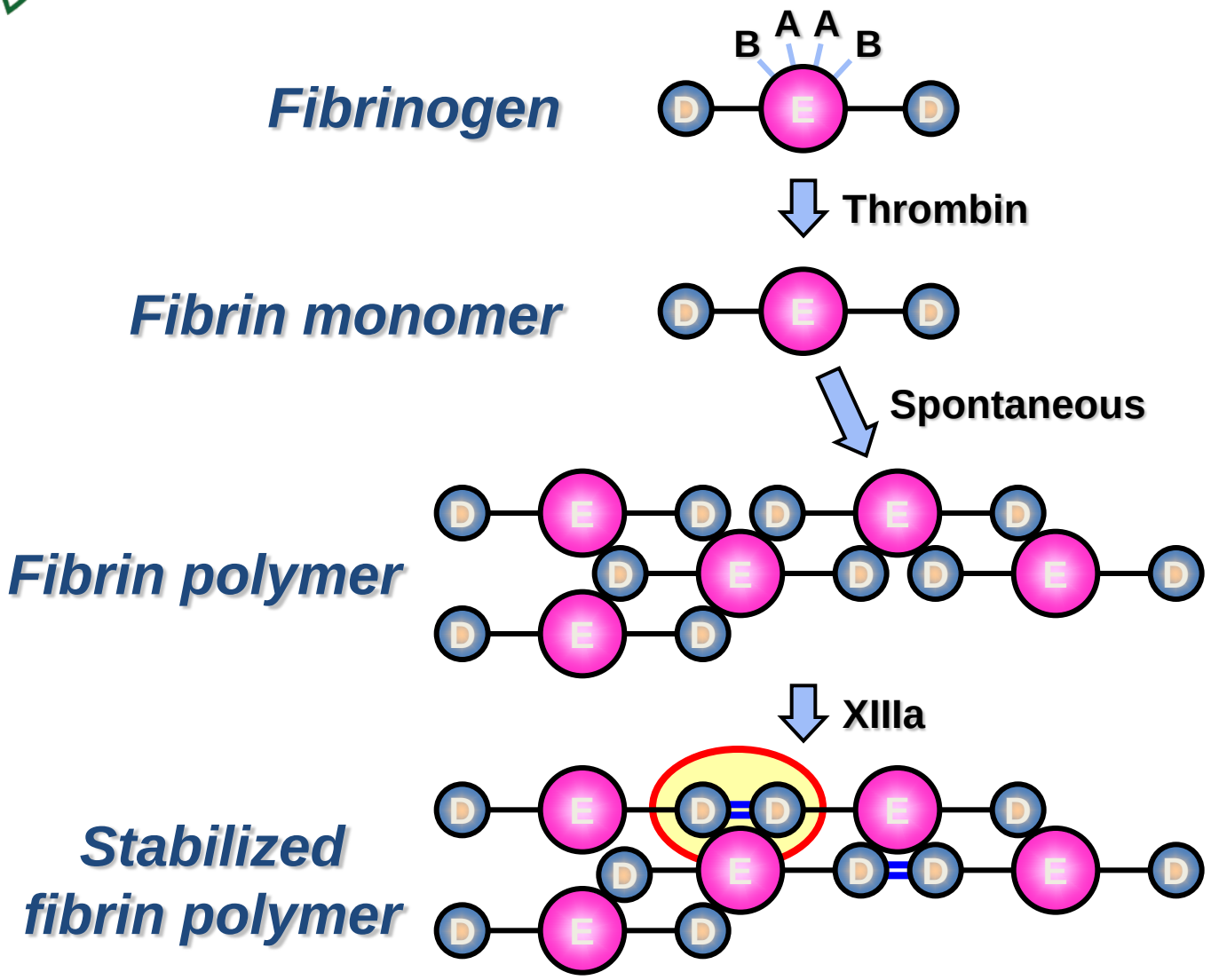
Formation of Fibrin Polymer



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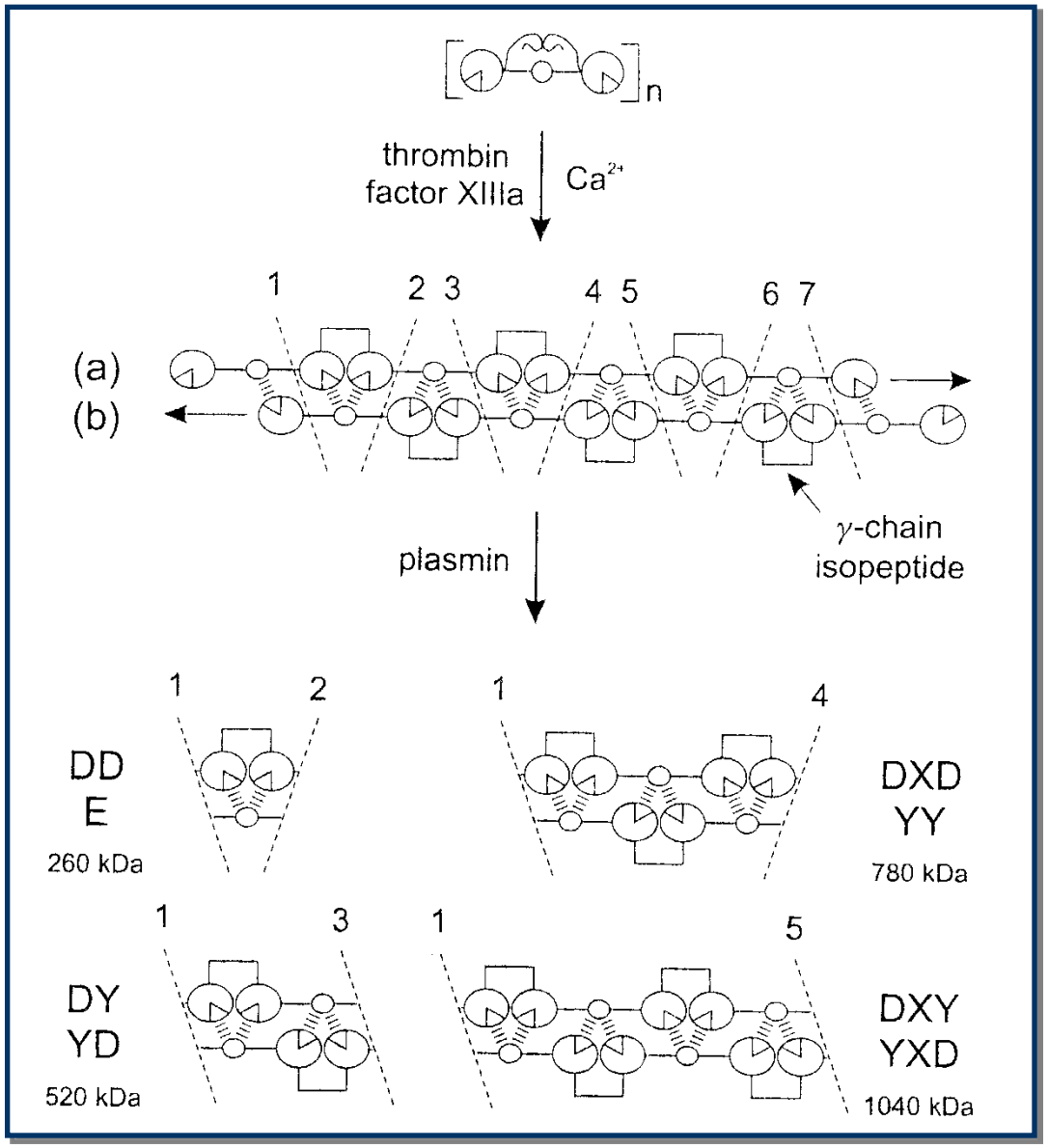
Degradation of fibrin



Walker et al;
JBC (1999); 274:
5201 - 5212

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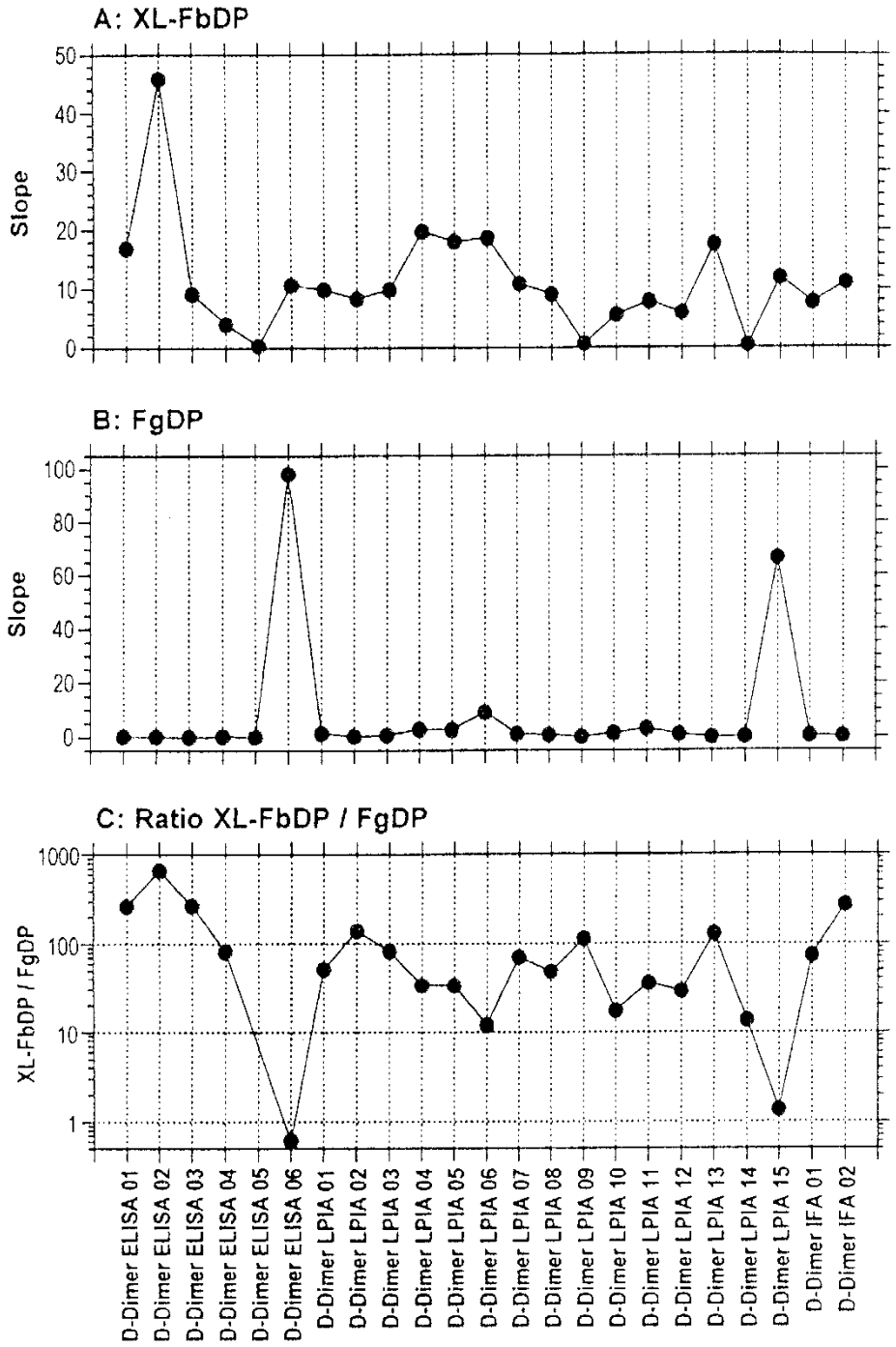

Dempfle et al., T&H 2001;85:671

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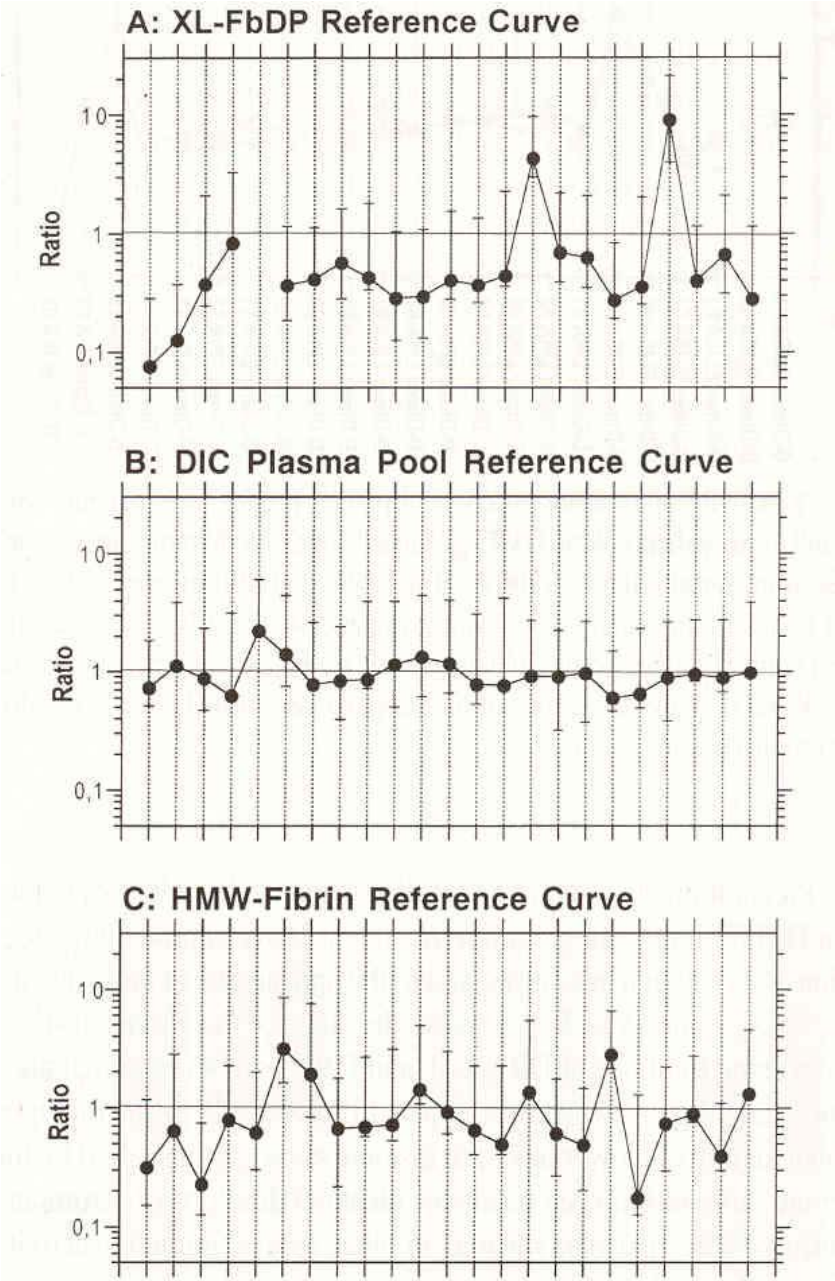

Dempfle et al., T&H 2001;85:671

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HISTORY

International Standard of purified D-Dimer	**FAILED**
International Standard of whole blood lysate	**FAILED**
International reference material of a pool of patient plasma samples	**FEASIBLE**

It appears feasible to generate a conversion factor for each of the "D-Dimer assays" studied, which will make widely varying results obtained with these kits comparable.

W. Nieuwenhuizen, TH 1997; 77: 1031 - 1033

Confirmed in the FACT study.

C.E. Dempfle et al, TH 2001; 85: 671 - 678

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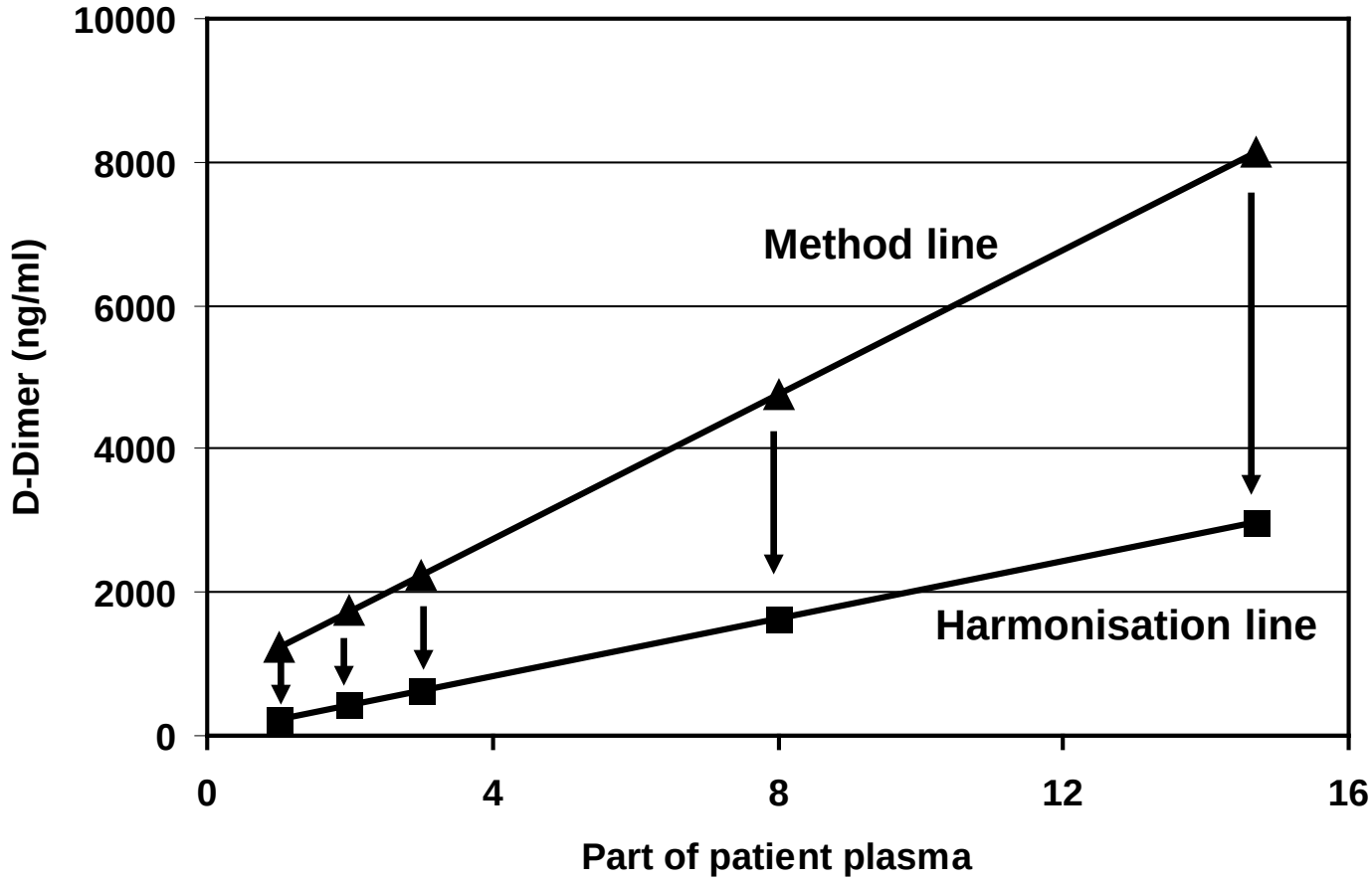
A model for the harmonisation of test results of different quantitative D-dimer methods

Piet Meijer[1,2], Frits Haverkate[1], Cornelis Kluft[2], Philippe de Moerloose[3], Bert Verbruggen[4], Michael Spannagl[5, 6]



Thromb Haemost 2006; 95: 567–72

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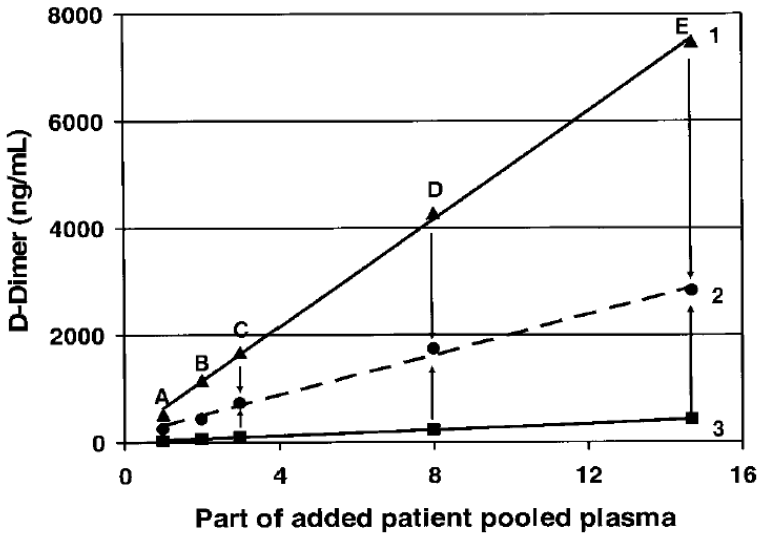
SAMPLE	Consensus value (mg/L)	CV (%) Before harmonization	CV (%) After harmonization
A	0.252	91.0	18.2
B	0.425	92.3	7.4
C	0.736	86.8	6.1
D	1.733	83.6	5.9
E	2.816	82.3	1.5

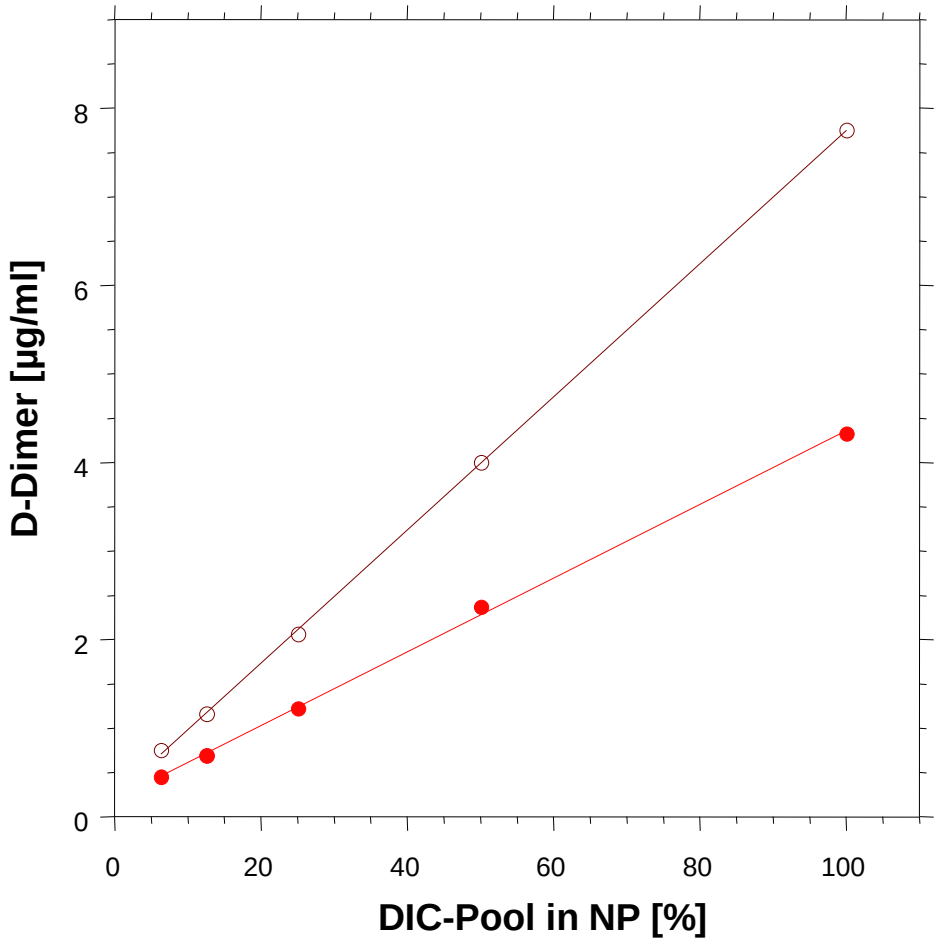
P. Meijer *et al*, TH 2006; 95: 567 - 572

The problem of a ‘consensus value‘: why we need a common calibrator

A model for the harmonisation of test results of different quantitative D-dimer methods

Piet Meijer[1,2], Frits Haverkate[1], Cornelis Kluft[2], Philippe de Moerloose[3], Bert Verbruggen[4], Michael Spannagl[5, 6]





All assays in FACT4 y = 0,24375 + 0,075103x R= 0,99992

Assays used by P.Meijer et al. y = 0,20833 + 0,041591x R= 0,99945

C.E Dempfle, ECAT participants Meeting 2006

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The calibrator

- **Fibrin degradation product D-dimer is NOT a suitable common primary calibrator for D-dimer assays**
- **The calibrator should contain a ‘physiological‘ array of crosslinked fibrin derivatives**
- **A pooled plasma from patients with high levels of D-dimer antigen is a suitable primary calibrator**
- **The calibrator may be diluted with assay-specific buffers, therefore only ONE calibrator (not a set of calibrators) is needed**

C.E Dempfle, ECAT participants Meeting 2006

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Harmonisation of D-dimer — A call for action

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23 September 2015

In summary, establishing D-dimer commutability among clinical samples should be regarded as an essential issue. We propose a concerted effort in recognising the current problems with the D-dimer assays in the lack of both standardisation and the need for harmonisation. A possible solution to these issues is to use a large number of samples from different clinical settings to produce a stable freeze dried reference preparation containing a high D-dimer concentration of heterogeneous species. This material could be diluted to generate a range of D-dimer values and construct a consensus reference line for different commercial assays, as previously demonstrated [10]. Working also with manufacturers of D-dimer assays, and not only with scientists and clinicians, may help the development of an easy to use reference material. Further efforts are also required to agree upon a common type and magnitude of D-dimer measurement unit.

Conclusions

- The loss of D-dimer antigen on storage of plasma (SS258) at elevated temperatures was not anticipated
- The rate of loss is difficult to predict from Arrhenius models
- The loss is consistent with theories of fibrin aggregation and cross-β structures formation
- D-dimer in patient plasma is likely to form non-reactive aggregates
- Trehalose is a promising excipient to stabilise FDP/D-dimer and prevent cross-β structure formation to help with standardisation

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EQAS indications for opportunities for improvement?

Almost every discipline in the medical laboratory field has problems related to standardisation and/or harmonisation!