

# **Das unerkannte von Willebrand Syndrom**

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**Hamburg**

# Offenlegung potentieller Interessenkonflikte

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## 1. Anstellungsverhältnis oder Führungsposition

keine

## 2. Beratungstätigkeit

keine

## 3. Aktienbesitz

keiner

## 4. Honorare

keine

## 5. Finanzierung wissenschaftlicher Untersuchungen

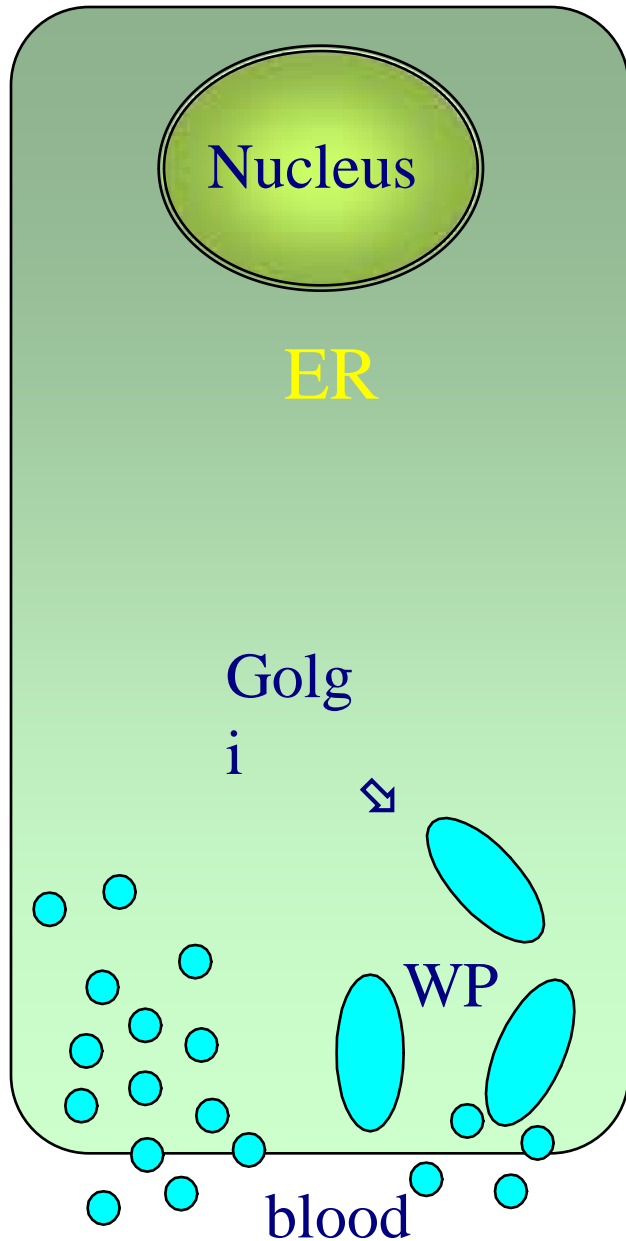
keine

## 6. Gutachtertätigkeit

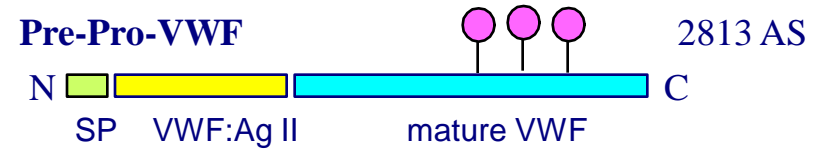
keine

## 7. Andere finanzielle Beziehungen

keine



**VWF-gene chromosome 12p13 178 Kbp**



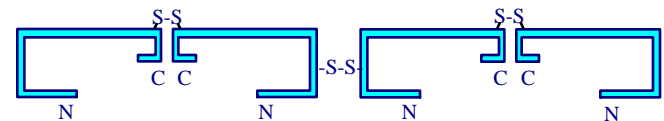
**C-terminal dimerisation**

**Pro-VWF-dimer**



**N-terminal multimerisation**

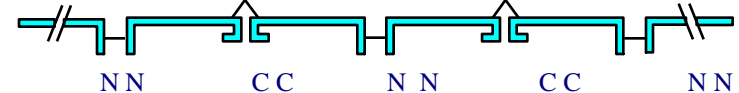
**Pro-VWF-multimer**



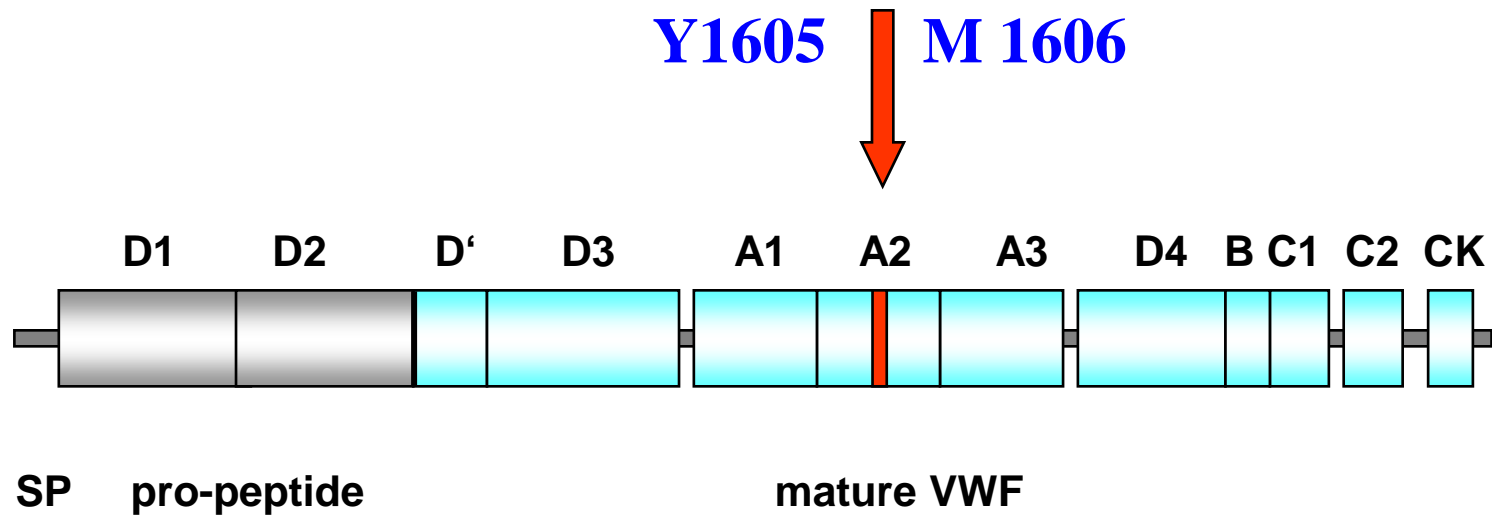
**Propeptide-cleavage**



**VWF-multimer** 0,6 - 20.000 KD



# von Willebrand-factor cleavage site



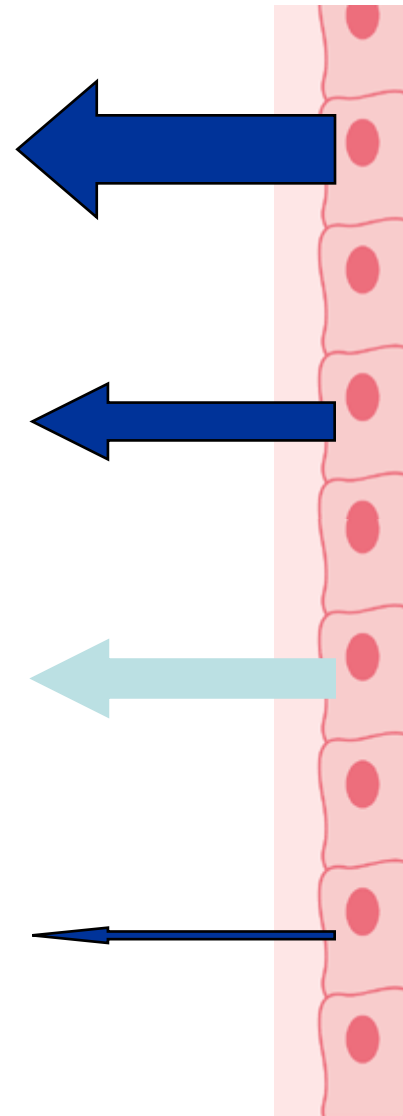
# VWD Comes in Three Varieties

Normal individual:  
normal VWF

Type 1: reduced quantity,  
essentially normal VWF  
70% of cases

Type 2: functionally deficient VWF  
25% of cases

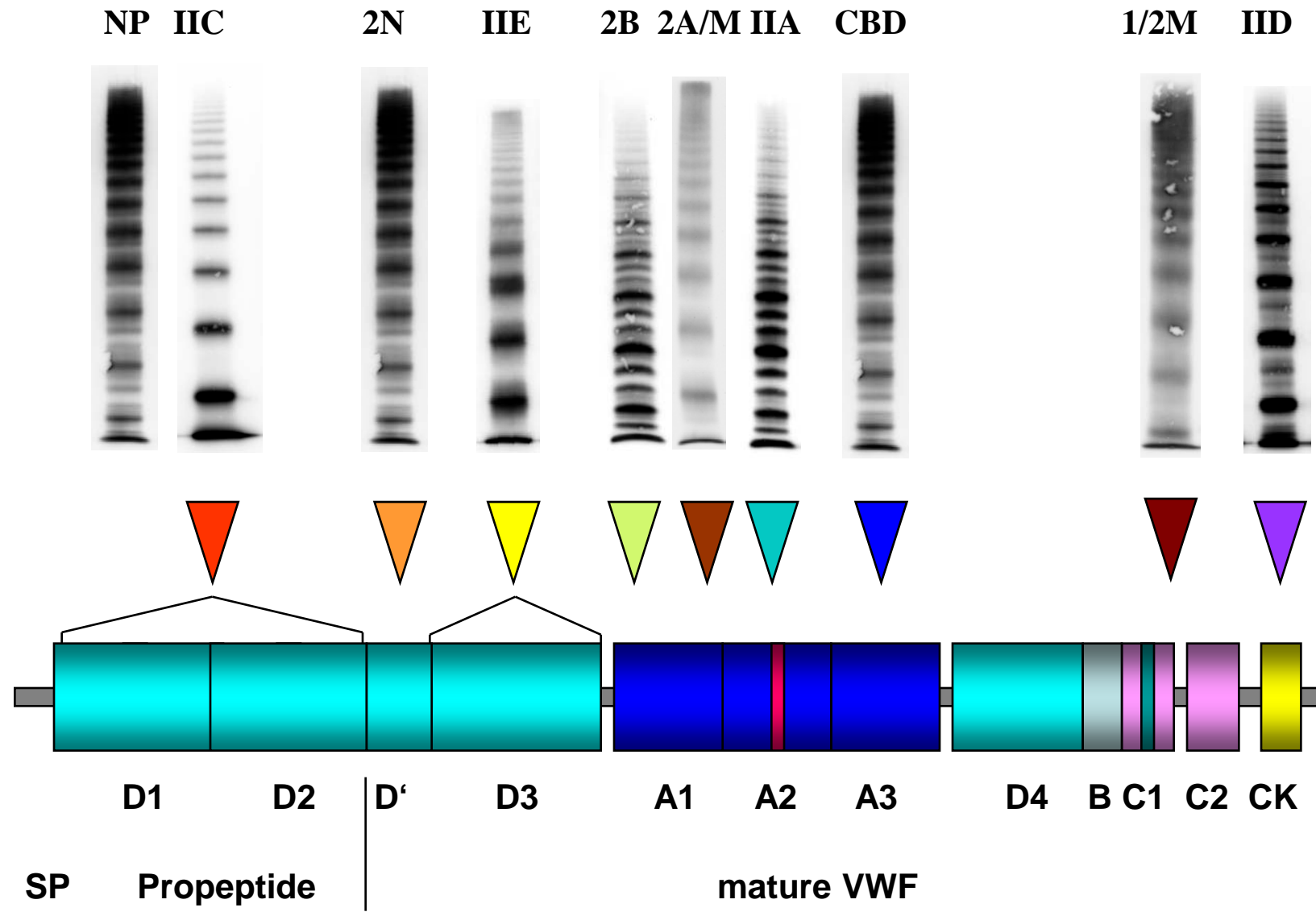
Type 3: virtually no VWF  
5% of cases



# Classification of VWD

- Type 1 refers to partial **quantitative** deficiency of VWF (weakened in the recent update)
- Type 3 refers to complete absence of VWF
- Type 2A refers to qualitative variants with decreased platelet-dependent function that is associated with the **absence** of high-molecular-multimers
- Type 2B refers to qualitative variants with increased binding to GP Ib
- Type 2M refers to qualitative variants with decreased platelet-dependent function that is **not caused by the absence** of high-molecular-multimers
- Type 2N refers to qualitative variants with severely decreased or absent F VIII binding capacity

Abb. 5



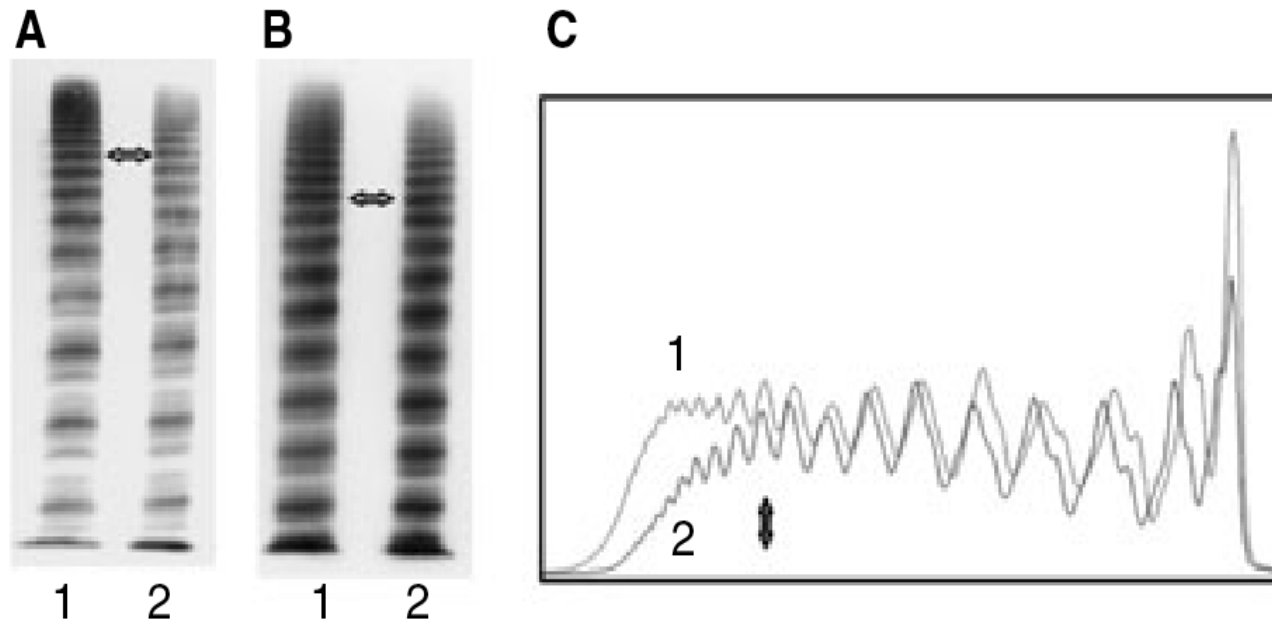
# **Reason I**

## **properties of the VWF**

- **Large reference range: 50 – 160%**
- **Sharp rise in acute situations (stress – small children; acute illness; exercise)**
- **Significant rise during pregnancy, malignancy, age >40**
- **Diagnosis at one occasion without repeat tests (usually 2-3)**
- **One test only and not the required battery of tests (VWF:Ag, VWF:RCo, VWF:CB, VWF:FVIIIB, multimers)**



# ABNORMAL VWF IN CV



VWF multimers after implantation of a left ventricular assist device

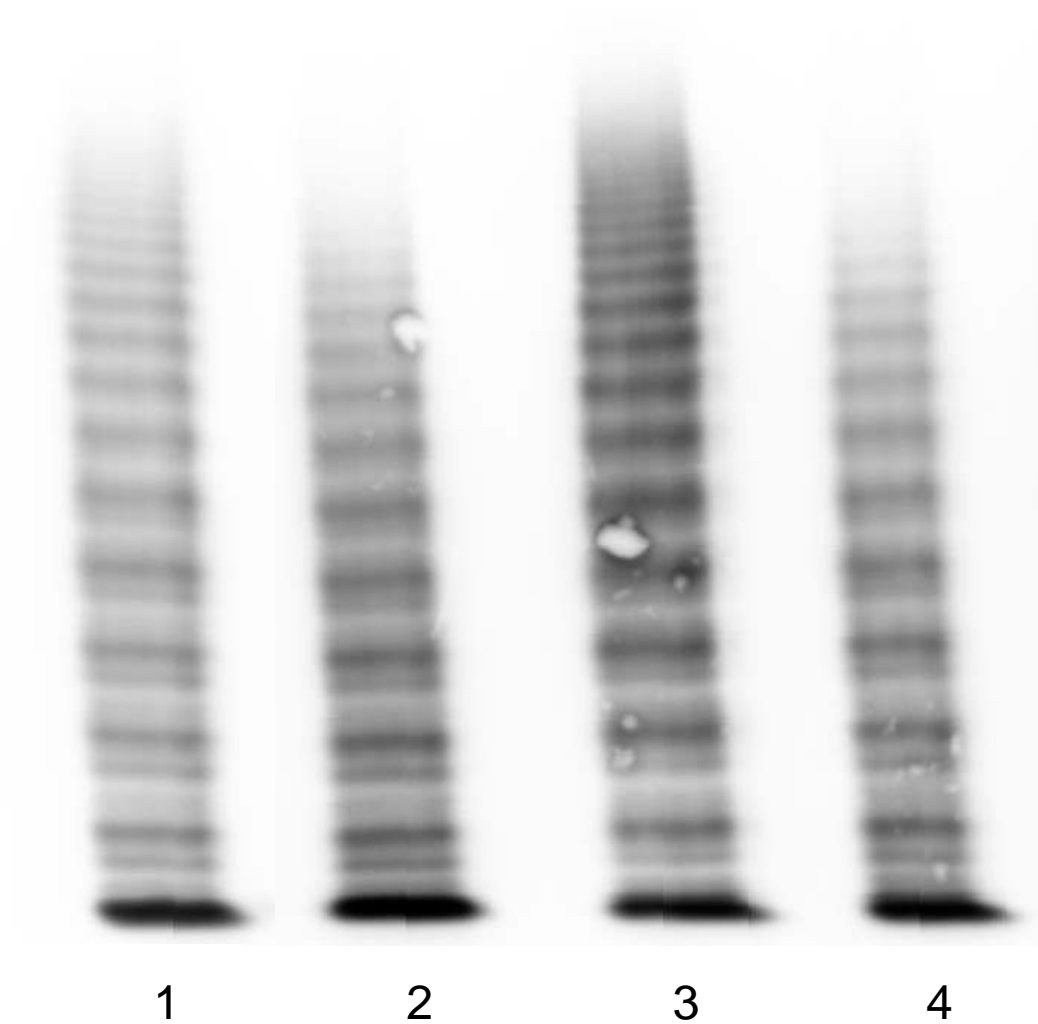
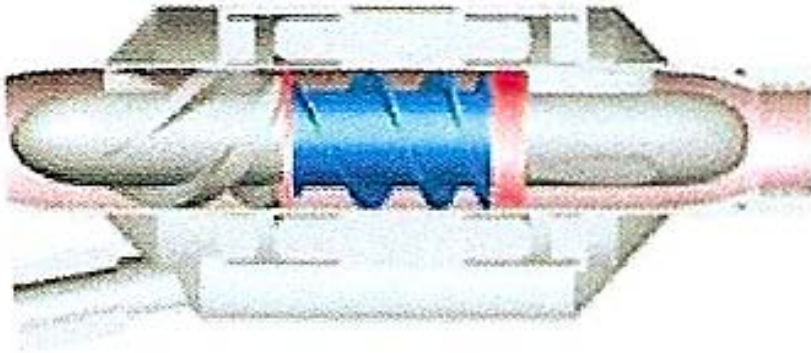
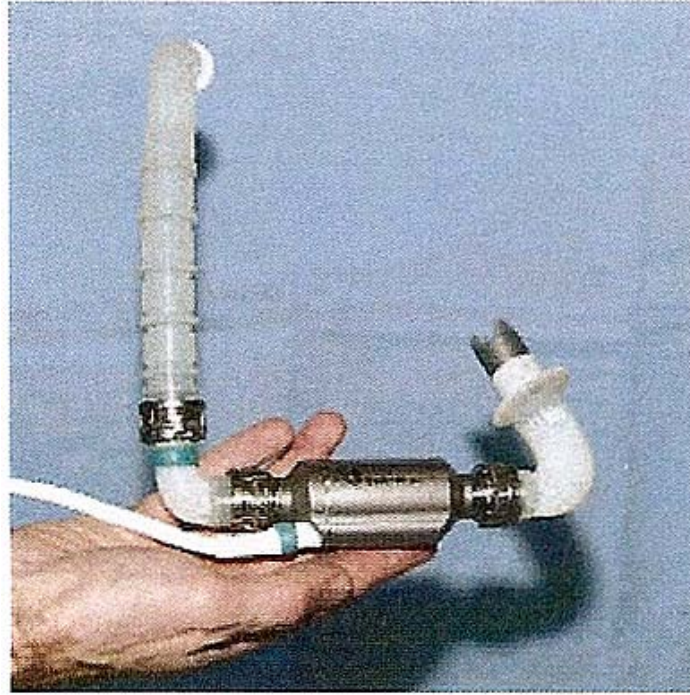
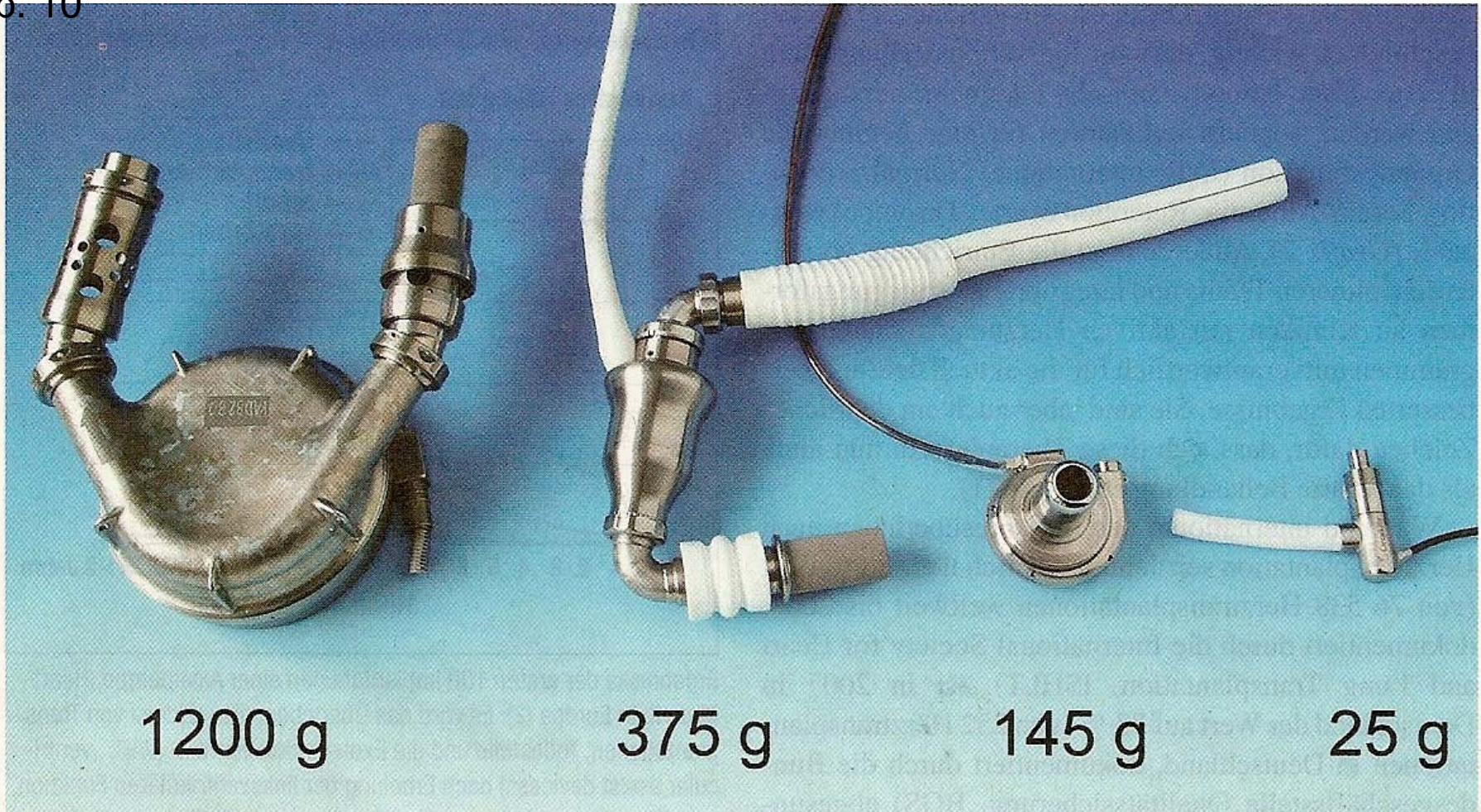


Abb. 9

# Berlin Heart Incor I





1200 g

375 g

145 g

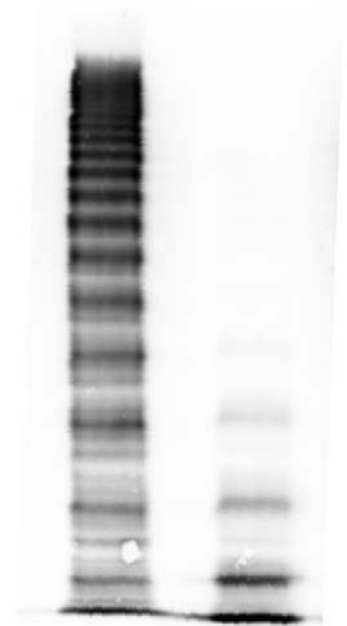
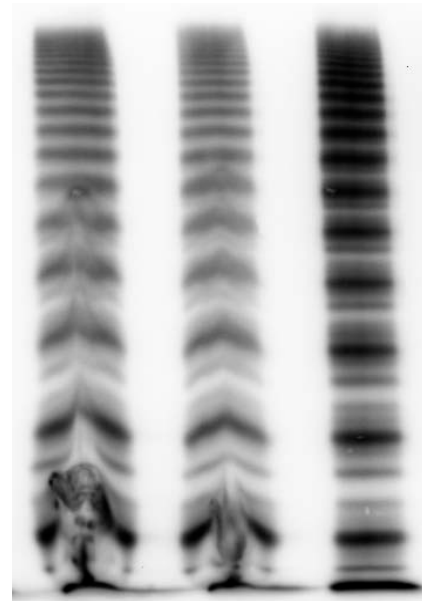
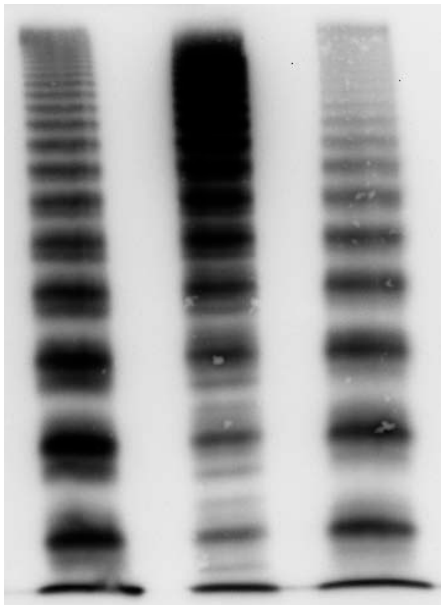
25 g

**Abbildung 3: Technische Entwicklung von linksventrikulären Unterstützungssystemen (Beispielhafte Produkte) von links nach rechts:**

- 1. Generation: pulsatile elektrisch angetriebenes VAD (VAD, „ventricular assist device“) (Thoratec HeartMate I)
  - 2. Generation: nicht pulsatile Axialpumpe (Thoratec HeartMate II)
  - 3. Generation: nicht pulsatile Zentrifugalpumpe (HeartWare HVAD)
  - 4. Generation: Miniatur LVAD (LVAD, „left ventricular assist device“) zur partiellen Kreislaufunterstützung (CircuLite Synergy)
- (Abdruck mit freundlicher Genehmigung von Thoratec Corporation/HeartWare, Inc./CircuLite, Inc.)

# increased clearance

- **Inherited: type 1, type 1 (2M) Vicenza, 2A (IIE = multimerization defect)**
- **Acquired: MGUS type IgG, myeloma**
- **MGUS type IgM, M. Waldenström**



# Reason III

## modern fast latex based tests may show wrong results

- Inherited and acquired: interference with rheuma factor
- Recent case: does monoclonal IgM alone or in complex with VWF interfere?



NP IgM kappa

VWF:Ag (ELISA) 58%

VWF:CB (ELISA) 2%

VWF:RCo (plt. agglut.) <10%

**VWF-act. (Latex) 400%**

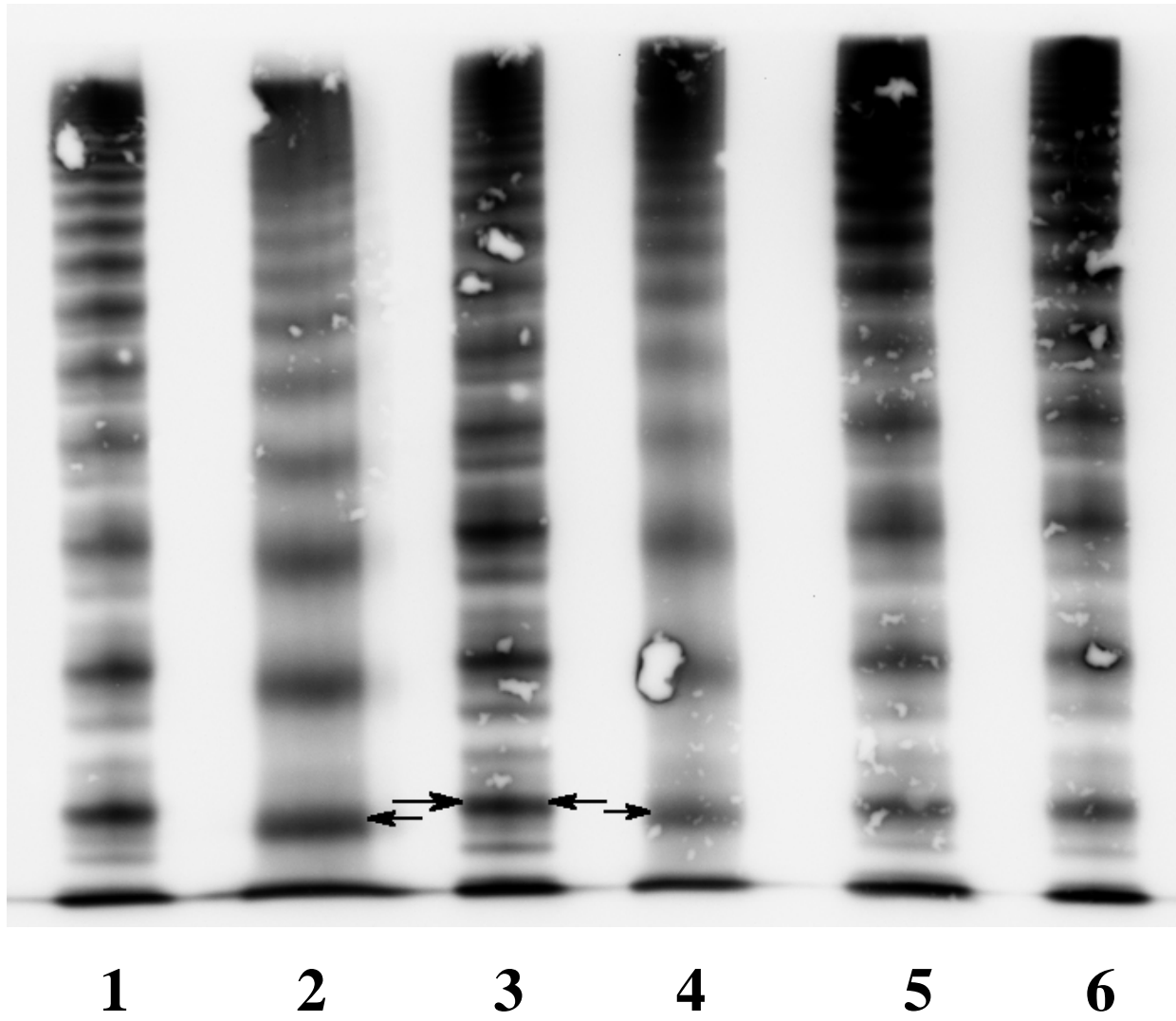
**VWF-GP Ib-bdg. (Latex) 84%**

# Reason IV

## mere structural defect: abnormal folding

- **Inherited: type 1 (smeary), more than 20% of these patients show a VWF:Ag >50%, some >100%: type 1??**
- **VWF:Ag = VWF:RCo = VWF:CB**
- **The functional defect of this variant is only expressed in the abnormal structure; functional test missing**
- **2009: 40 patients**

Abb. 14





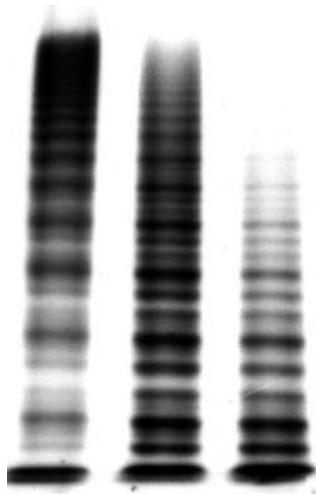
# **Reason V**

## **missing communication**

- **„Order entry“**
- **Acute severe bleeding in a female type 2A patient: F IX and multiplate aggregation**
- **FVIII inhibitor in a patient with acquired VWD type 2 with a monoclonal IgG paraprotein**
- **Sometimes a thrombosis screen in acute bleeding patients**

# Acknowledgement

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