VII Giornate Ematologiche Vicentine

Vicenza, 10-12 Ottobre 2016

Come misuro la gravità del sintomo emorragico

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Divisione di Ematologia

Vicenza

Bleeding disorders are heterogeneous

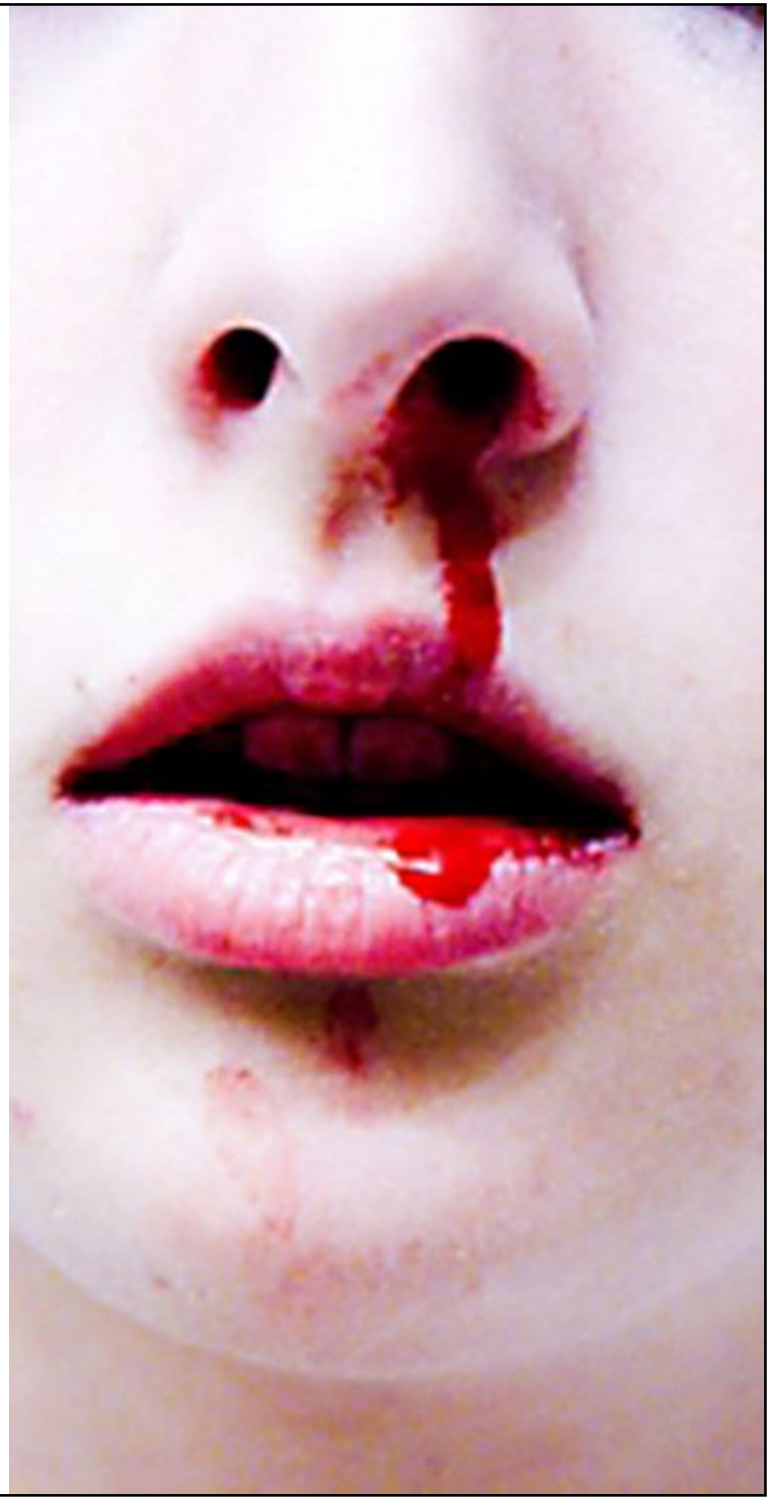
- Mild Bleeding Disorders:
  - Bleeding symptoms reduce QoL, but do not threaten patient life or cause permanent damage
- Severe Bleeding Disorders:
  - Bleeding symptoms may threaten patient life or cause permanent damage if not adequately treated

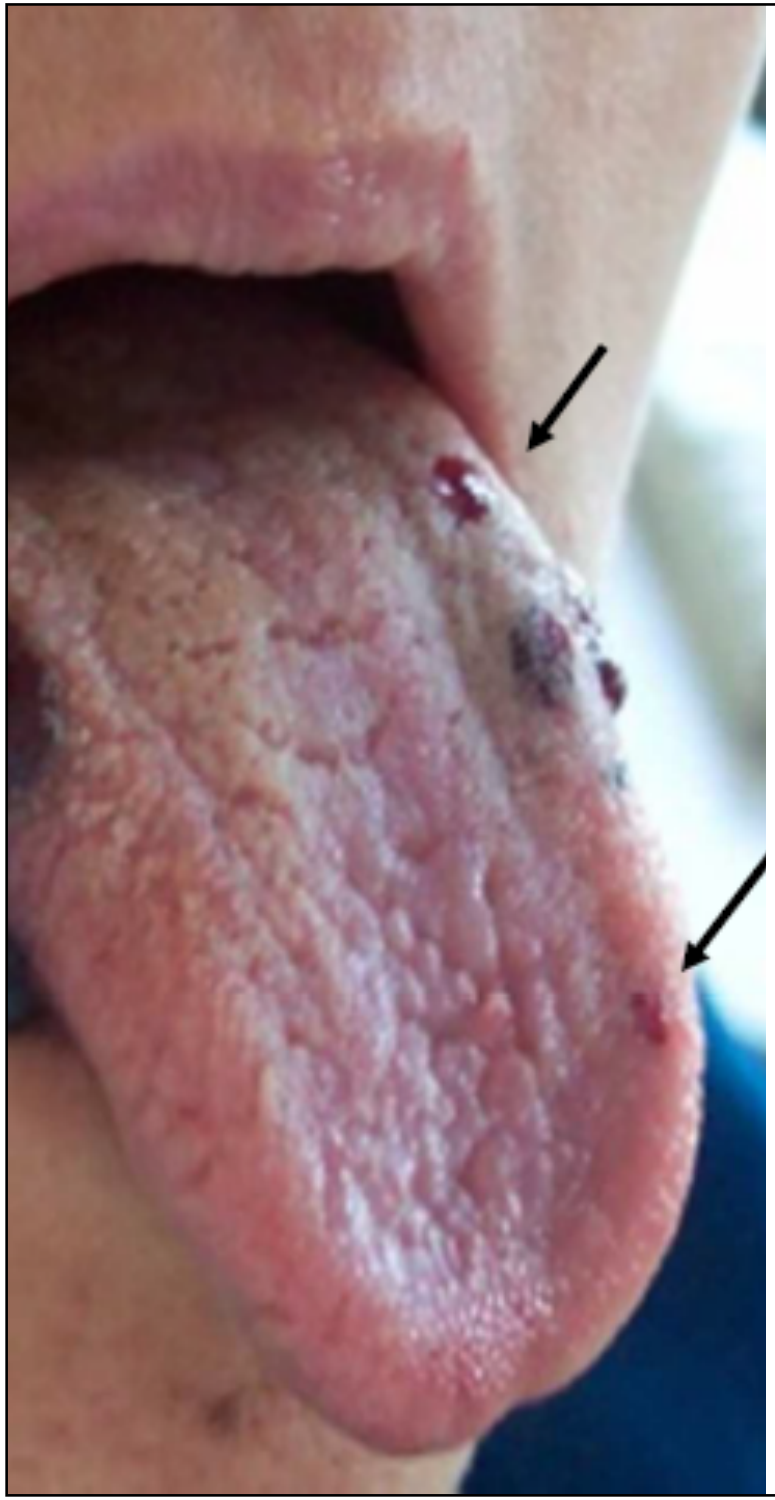
Causes of bleeding are heterogeneous

- Congenital BD:
  - Bleeding symptoms present since childhood, variable phenotype
- Acquired BD:
  - Late appearance, sometimes related to use of antiplatelet/ anticoagulant drugs.
  - Mostly mild.
- “Chance” bleeding
  - E.g. peri-surgical or post-partum bleeding (1-3 events per 100 procedures)

Why measuring bleeding severity: diagnosis

- The patient is referred because of some bleeding symptom or clotting abnormality
- Has the children VWD?



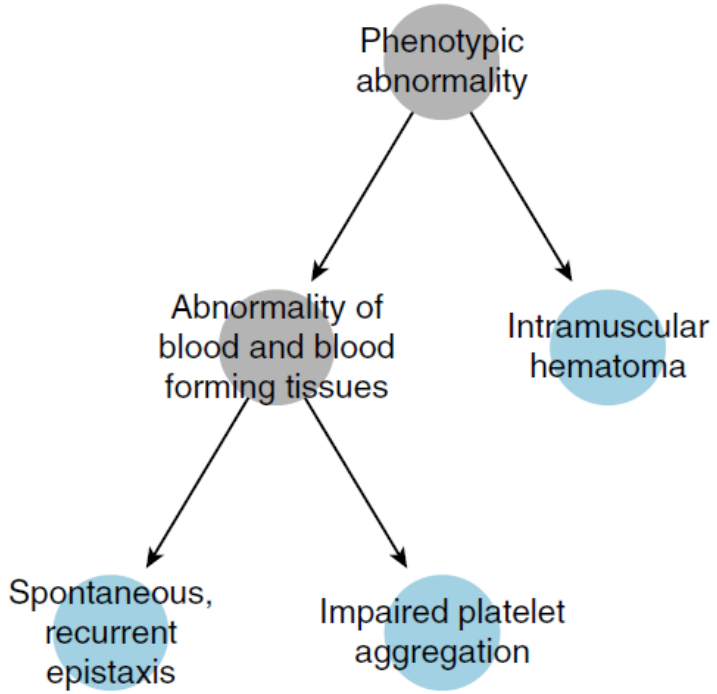


Why measuring bleeding severity: prognosis/therapy

- Does this ITP patient warrant more aggressive therapy?

Why measuring bleeding severity: research

Detailed characterization of bleeding phenotype required for genetic association studies



Simeoni et al. Blood, 2016.

Clinical assessment of bleeding

J Clin Epidemiol Vol. 42, No. 8, pp. 711–718, 1989
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THE BLEEDING SEVERITY INDEX: VALIDATION AND COMPARISON TO OTHER METHODS FOR CLASSIFYING BLEEDING COMPLICATIONS OF MEDICAL THERAPY*

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Clinical assessment of bleeding

- Implicit methods
  - Personal judgement (gestalt)

Landefeld et al. Journal of clinical epidemiology, 1989.

Gestalt – a theory of perception

Our minds organize information to a global perception rather than by assessing each individual element

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Gestalt in bleeding disorders: Syndromic reasoning

Bleeding symptoms	Platelet defects	Clotting factor deficiencies
Overview of bleeding events	Mucocutaneous bleeding	Deep tissue bleeding
Excessive bleeding after minor cuts	Yes	Not usually
Petechiae	Common	Uncommon
Ecchymoses	Generally small and superficial	May develop large subcutaneous and soft tissue hematomas
Hemarthroses, muscle hematomas	Uncommon	Common in severe deficiency states
Bleeding with invasive procedures, including surgery	Often immediate, with degree of bleeding dependent upon the severity of the defect	May be associated either with procedural bleeding or delayed bleeding, depending upon the type and severity of the defect

Clinical assessment of bleeding

- Implicit methods
  - Personal judgement (gestalt)
- "Old" explicit methods
  - Adherence to stated definitions

Landefeld et al. Journal of clinical epidemiology, 1989.

The WHO criteria

TABLE 1. Recommendations for Grading of Acute and Subacute Toxicity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic (Adults)					
Hemoglobin (g/100 ml)	≥11.0	9.5–10.9	8.0–9.4	6.5–7.9	<6.5
Leukocytes 1000/cmm	≥4.0	3.0–3.9	2.0–2.9	1.0–1.9	<1.0
Granulocytes 1000/cmm	≥2.0	1.5–1.9	1.0–1.4	0.5–0.9	<0.5
Platelets 1000/cmm	≥100	75–99	50–74	25–49	<25
Hemorrhage	none	petechiae	mild blood loss	gross blood loss	debilitating blood loss

Miller et al. Cancer, 1981.

Clinical assessment of bleeding

- Implicit methods
  - Personal judgement (gestalt)
- "Old" explicit methods
  - Adherence to stated definitions
- Bleeding severity indexes
  - Based on criteria for amount, rate, and consequences of bleeding

Landefeld et al. Journal of clinical epidemiology, 1989.

Bleeding severity index

Table 1. Summary of the criteria used in the bleeding severity index

*Amount of blood loss**
- Severe†: ⩾3 units
- Moderate†: ⩾2 units and <3 units
- Mild†: ⩾1 unit and <2 units

Rate of bleeding
- Acute: <3 days
- Subacute: 3–7 days
- Chronic: >7 days

Consequences of bleeding
- Fatal: death
- Life-threatening: serious permanent injury such as myocardial infarction, stroke; surgery to stop bleeding
- Potentially life-threatening: 2 or 3 of the following:
  - —severe blood loss
  - —hypotension‡
  - —critical anemia§

Landefeld et al. Journal of clinical epidemiology, 1989.

Sintomi emorragici

- Maggiori
  - Emorragia fatale
  - In zone critiche (intracranica, intraspinale, intraoculare, retro-peritoneale, emartro, intramuscolare con sdr. compartimentale)
  - Calo Hb ≥ 2 g/dL
  - Richiedente trasfusione ≥ 2 RBC units

Schulman et al, JTH 2005

Sintomi emorragici

- Minori
  - Clinicamente manifesti, ma non soddisfacenti i criteri di em. maggiore
  - Non richiedono ospedalizzazione
  - Abbastanza severi da interferire con le attività sociali (es., lavoro) e la qualità della vita

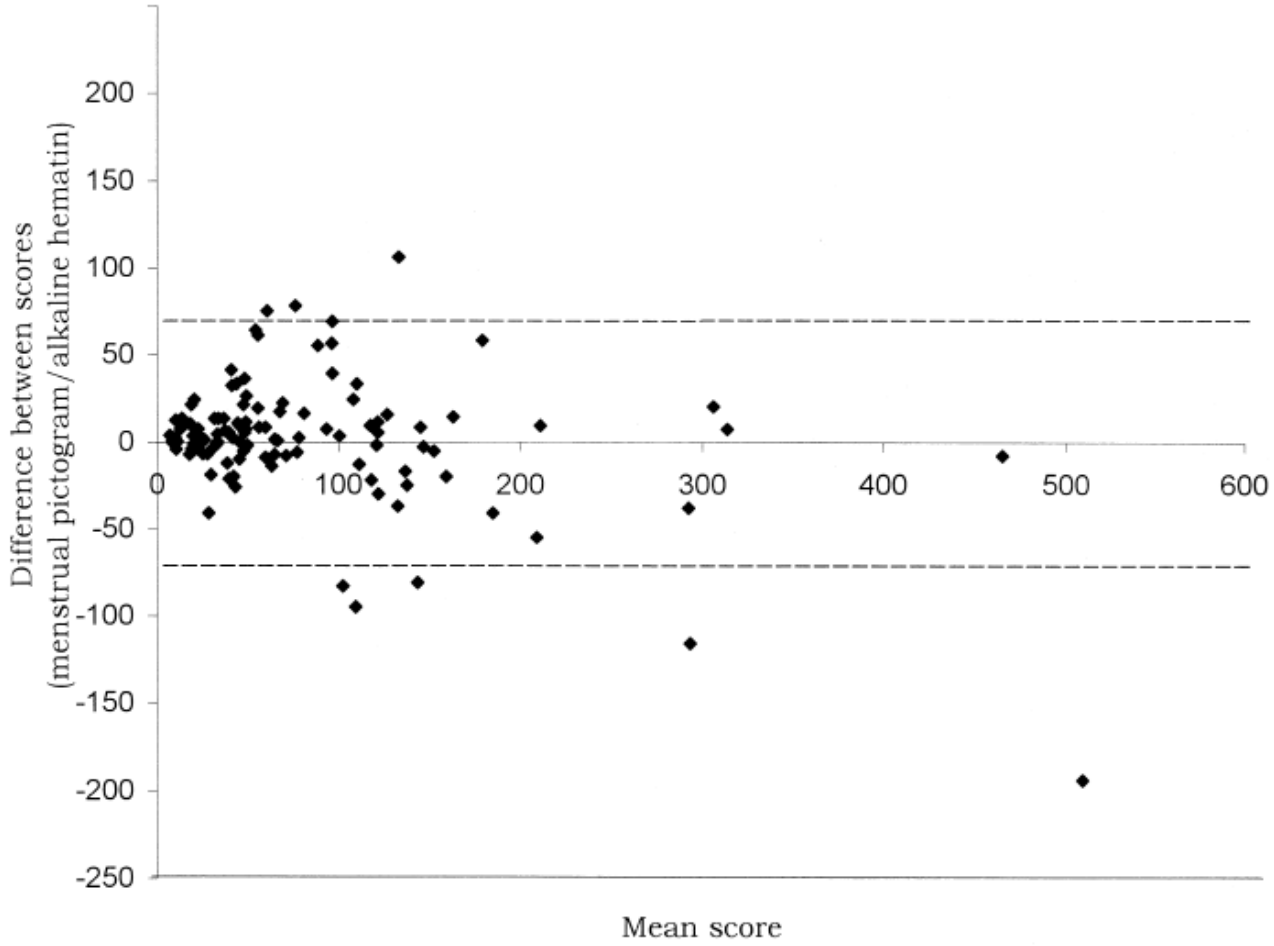
Graafsma et al, Throm Haemostas 1997
Knight et al, Haemophilia 2003
Rodeghiero et al, JTH 2010

Properties of a bleeding scale

- Reliable (intra/inter-observer consistency)
- Accurate
- Outcomes should be related to the intensity of bleeding as assessed by the scale

Koreth et al. Transfusion, 2004.

Scales are proxys for relevant outcomes



Wyatt et al. Fertil Steril, 2001.

Some quantitative bleeding scales

Scale	Clinical setting	Refs
PBAC	Assessment of menstrual blood loss only	*Higham et al. Br J Obstet Gynaecol, 1990.*
Rebulla	Acute bleeding in a single trial	*Rebulla et al. N Engl J Med, 1997.*
ITP	Recent bleeding in ITP patients	*Buchanan et al. J Pediatr, 2002.*
SMOG	Recent bleeding in ITP patients	*Rodeghiero et al. Blood, 2013.*
Hemophilia severity score	Measure severity of hemophilia by number of hemorrhages and concentrate use	*Schulman et al. J Thromb Haemost, 2008.*
BMT bleeding	Bleeding after BMT	*Nevo et al. Blood, 1998.*
ISTH-BAT	Lifelong bleeding in MBD	*Rodeghiero et al. J Thromb Haemost, 2010.*

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No single scale useful for all scenarios.
Very few underwent external validation.

Choosing a bleeding scale

- Symptom-specific?
  - Trade accuracy for feasibility
- Disease-specific?
  - E.g., ITP or Hemophilia
- Setting?
  - Acute bleeding (e.g., post-surgical)
  - Lifelong bleeding (e.g., mild bleeding disorders)

Bleeding Scores and the diagnosis of MBD

- Tools to evaluate the life-long bleeding tendency
- Useful for
  - Standardization of data collection
  - Data sharing
  - Definition of the minimal bleeding history required to start laboratory diagnosis (high NPV)
  - Risk stratification

Standardization of data collection

ISTH 2010 criteria

SYMPTOMS (up to the time of diagnosis)	SCORE				
	0§	1§	2	3	4
Epistaxis	No/trivial	- > 5/year or - more than 10 minutes	Consultation only*	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy (use of hemostatic blood components and rFVIIa) or desmopressin
Cutaneous	No/trivial	For bruises 5 or more (> 1cm) in exposed areas	Consultation only*	Extensive	Spontaneous hematoma requiring blood transfusion
Bleeding from minor wounds	No/trivial	- > 5/year or - more than 10 minutes	Consultation only*	Surgical hemostasis	Blood transfusion, replacement therapy, or desmopressin

Rodeghiero et al. J Thromb Haemost, 2010.

1. Epistaxis

1.1	Have you ever had spontaneous epistaxis?	☐ Yes	☐ No or trivial (skip to 2)
1.2	Have the symptom ever required medical attention ?	☐ Yes	☐ No (resolve spontaneously; skip to 1.6)
1.3	If answer to 1.2 is yes, please specify	☐ Consultation only ☐ Cauterization ☐ Packing ☐ Antifibrinolytics ☐ Iron therapy ☐ Treatment with desmopressin ☐ Treatment with plasma ☐ Treatment with platelet concentrate ☐ Treatment with factor concentrates ☐ Blood (RBC) transfusion	
1.4	How many times in your life did you receive any of the above treatments (# 1.3)?	☐ 1 - 2 ☐ 3 to 5 ☐ 6 to 10 ☐ more than 10	
1.5	At what age did you first have symptoms?	☐ Before 1 year ☐ Between 1-5 years of age ☐ Between 6-12 years of age ☐ Between 13-25 years of age ☐ After 25 years of age	
1.6	Approximate number of episodes NOT requiring medical attention	☐ less than 1 per year ☐ 1 per year ☐ 2-5 every year ☐ 1-3 every month ☐ 1 every week	
1.7	Duration of average single episode (min.) NOT requiring medical attention	☐ 1 minute or less ☐ 1 - 10 minutes ☐ more than 10 minutes	

Data sharing…

厚労科研「出血性後天性凝固異常症」研究班

ISTH/SSC 出 血 評 価 票 （日本語試用版*1）

症例の 匿名化暗号: 調査年月日: 性別: 生年月:

評価時（何れかに○） 最重症期・ 初診時 ・ 診断時・ 治療前 ・ 治療後 ・ 治癒後 ・寛解後 ・ 退院時／現在

症状	出 血 ス コ ア				
	0	1	2	3	4
鼻出血	無し か 軽微	・年5回以上 か ・10分間以上	診察／検査のみ	パッキング か 焼灼術 か 抗線溶薬	輸血 か 補充療法（止血因子、rFVIIaの使用）（か デスモプレッシン）*2
皮膚の（出血）	無し か 軽微	露出部に年5回以上の挫創（1cm以上）	診察／検査のみ	広範囲	自発性血腫で輸血が必要
軽度外傷からの出血	無し か 軽微	・年5回以上 か ・10分間以上	診察／検査のみ	手術による止血	輸血 か 補充療法（か デスモプレッシン）
口腔（内出血）	無し か 軽微	有り	診察／検査のみ	手術による止血 か 抗線溶薬	輸血 か 補充療法（か デスモプレッシン）
胃腸管出血	無し か 軽微	有り（潰瘍、門脈圧亢進症、痔、血管形成異常に伴わない）	診察／検査のみ	手術による止血 か 抗線溶薬	輸血 か 補充療法（か デスモプレッシン）

BATs for the diagnosis of MBD

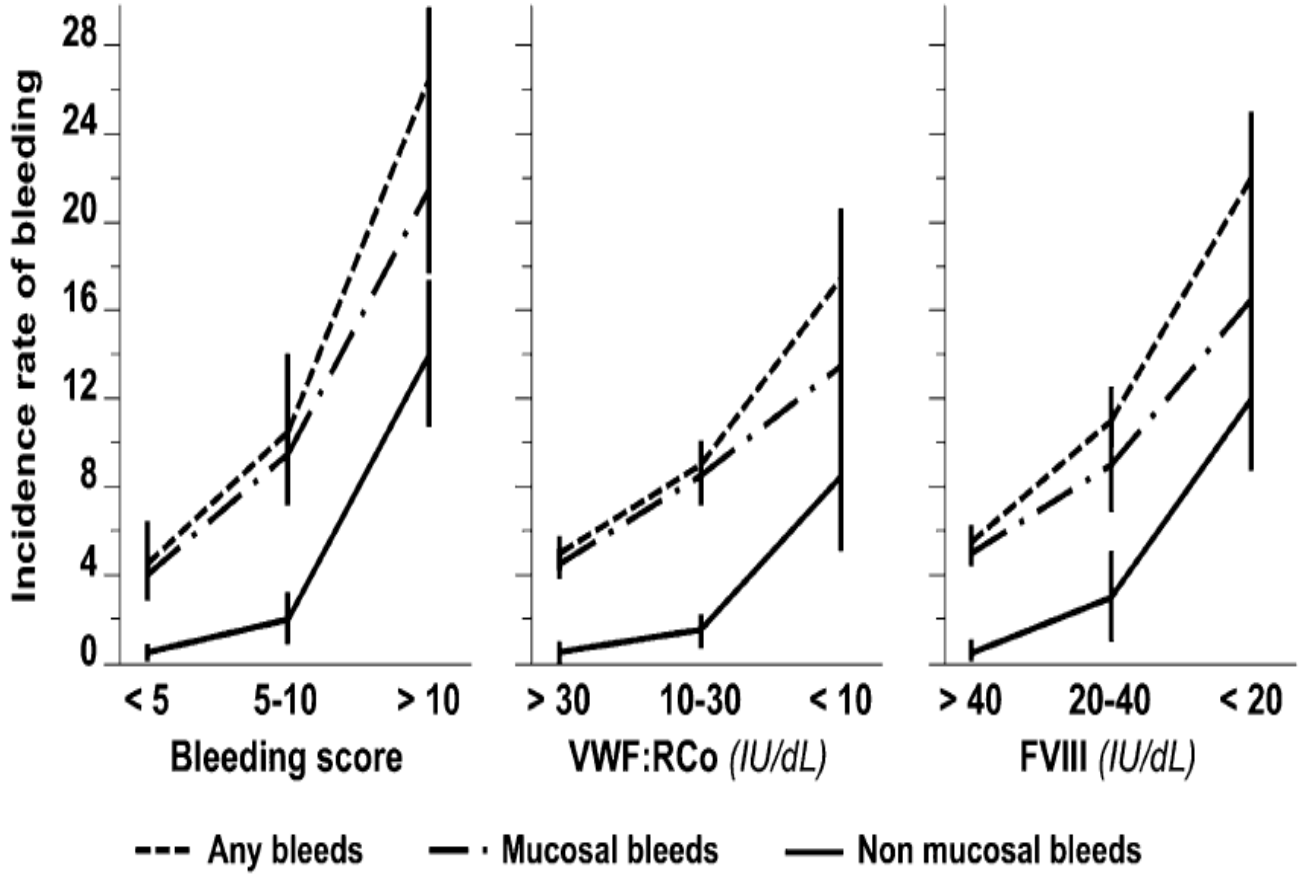
	Sensitivity	Specificity	PPV	NPV
VWD				
Rodeghiero, 2005	64.2	99.1	41.1	99.6
Bidlingmaier, 2012	65.2	94.6	83.3	86.9
Any MBD				
Tosetto, 2011	41.1	81.0	34.6	84.5
Bidlingmaier, 2012	47.7	94.6	87.5	69.7

- High NPV, useful to *exclude* presence of MBD
- Sensitivity around 50 - 60% for the diagnosis of MBD
- Laboratory investigation always needed
  - in very young, asymptomatic patients
  - in patients with an abnormal bleeding score

Tosetto et al, JTH 2011
Bidlingmaier, JTH 2012

Does BS correlate with bleeding risk?

Prospective follow-up of 797 italian VWD patients



Federici et al, Blood 2014

Conclusions

- Accurate quantitation of bleeding severity is relevant for both the patient and the clinician
- Bleeding scores are a useful way of integrating *quantitative* clinical *and* laboratory data
- Such approach will be even more important as NGS molecular information will become available in the next years
- Possibile prognostic role
- Several scales are available, but few validated