SIEMENS Healthineers

Rethinking Platelet Aggregation

Integrated, standardized, available.

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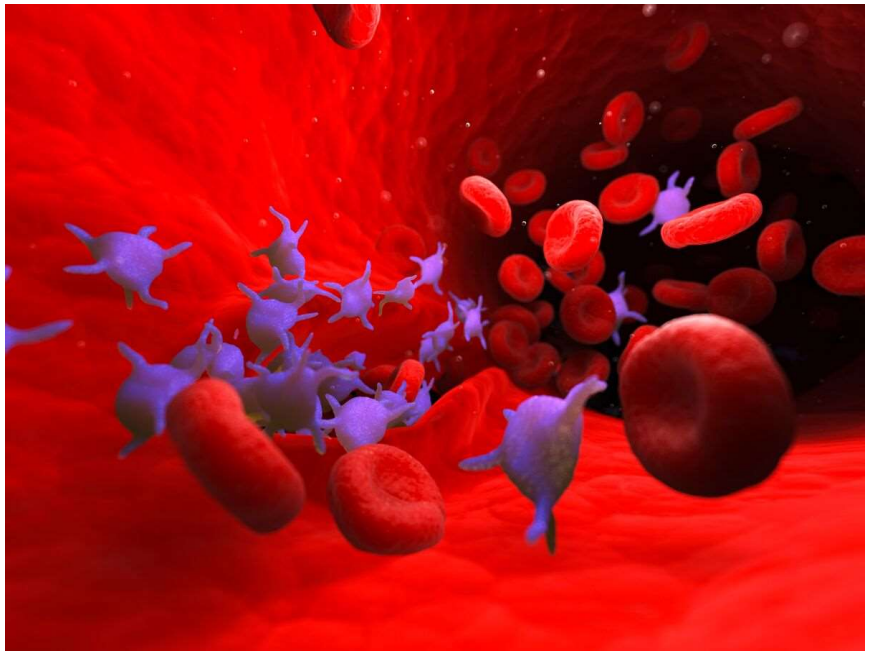
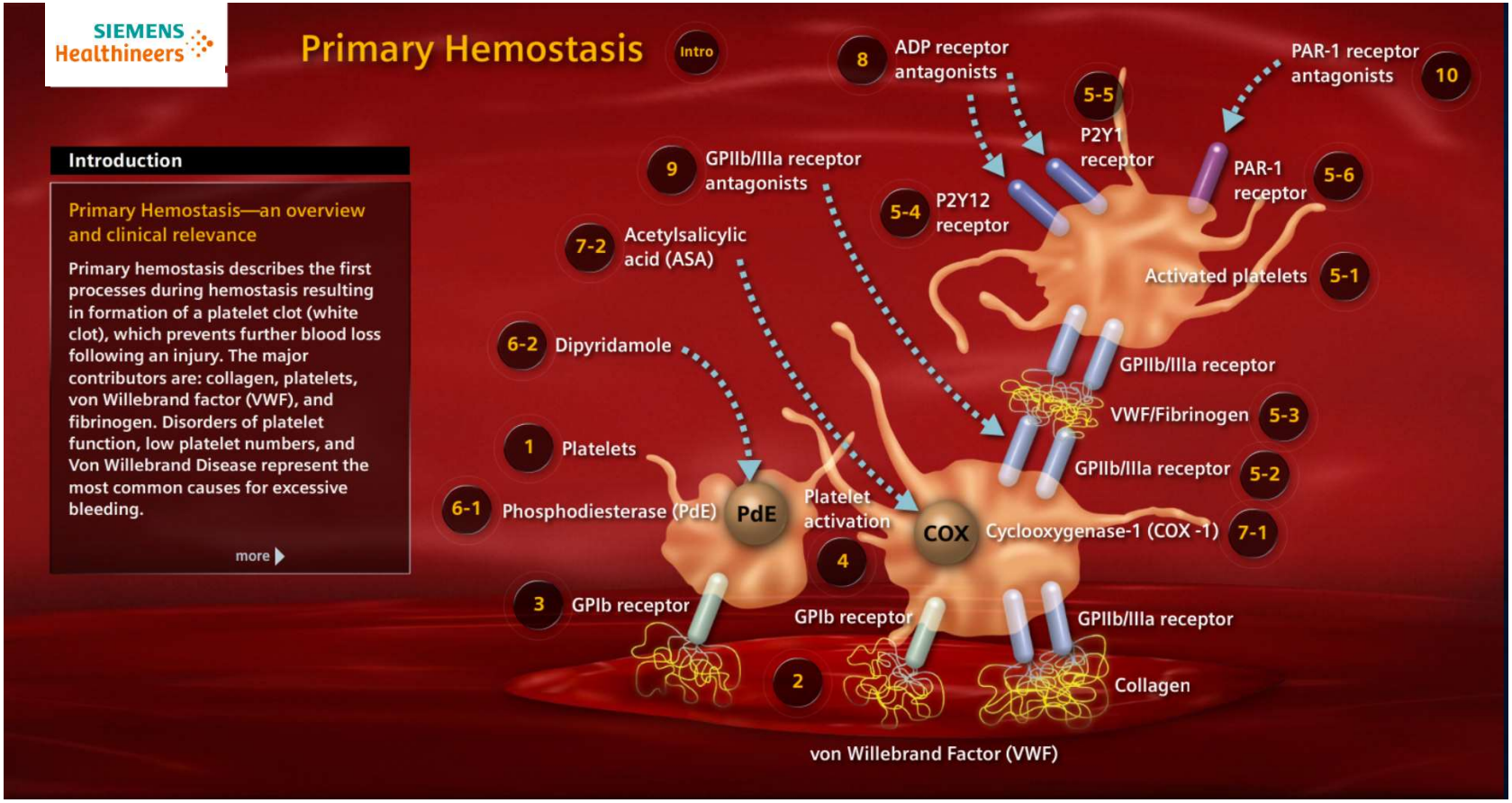
What are platelets?

What are platelets?

- Smallest blood cells: size 1–2 µm in diameter
- Shaped like a lense (inactive)
- Produced in bone marrow by megakaryocytes
- Lifespan about 5–10 days
- Normal platelet count ranges from 150,000 to 450,000/µL
- Degraded in liver and spleen by macrophages
- Functions: primary hemostasis, surface for secondary hemostasis, clot retraction



The role of platelets in primary hemostasis



Why is platelet testing so important?

Thrombocytopathy is the most common cause of bleeding

throm·bo·cy·top·a·thy (throm'bō-sī-top'ă-thē)

General term for any disorder of the coagulating mechanism that results from dysfunction of the blood platelets.

Medical Dictionary for the Health Professions and Nursing © Farlex 2012

Source: Scharf RE. Drugs that affect platelet function. Semin Thromb Hemost. 2012;38(8):865-83. doi: 10.1055/s-0032-1328881 Epub 2012 Oct 30.

Inherited vs. acquired thrombocytopathy

Inherited

- Much less frequent
- Can lead to severe bleeding
- Often not diagnosed
- Most common: von Willebrand disease
- Other rare disorders include Glanzmann thrombasthenia, Bernard-Soulier syndrome, and Delta (δ)-storage pool disease

Acquired

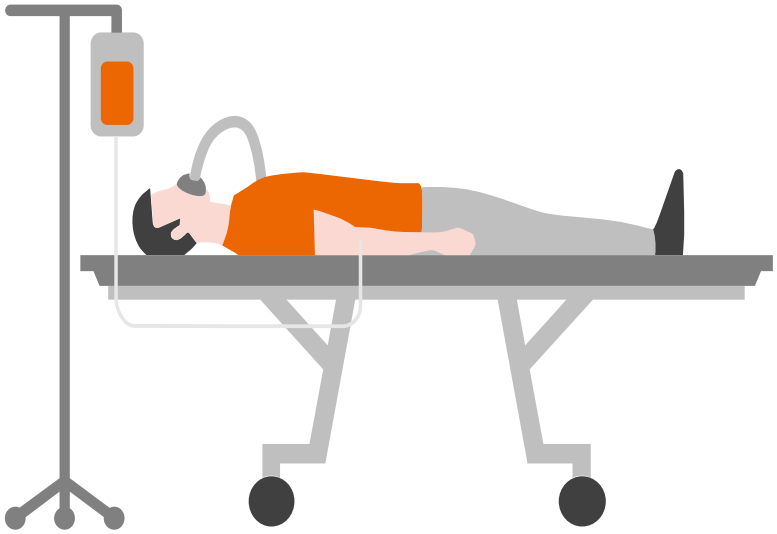
- More frequent
- Most common drugs are aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), along with antiplatelet drugs
- Diseases including cirrhosis, multiple myeloma, kidney disease, and lupus

Source: Scharf RE. Drugs that affect platelet function. Semin Thromb Hemost. 2012;38(8):865-83. doi: 10.1055/s-0032-1328881 Epub 2012 Oct 30.

7% of acutely hospitalized patients show thrombocytopenia at admission[1,2]

Possible symptoms[1]

- Severe bleeding episodes after surgery or injuries
- Hematoma/epitaxis
- Menorrhagia
- Bleeding in the skin/petechiae

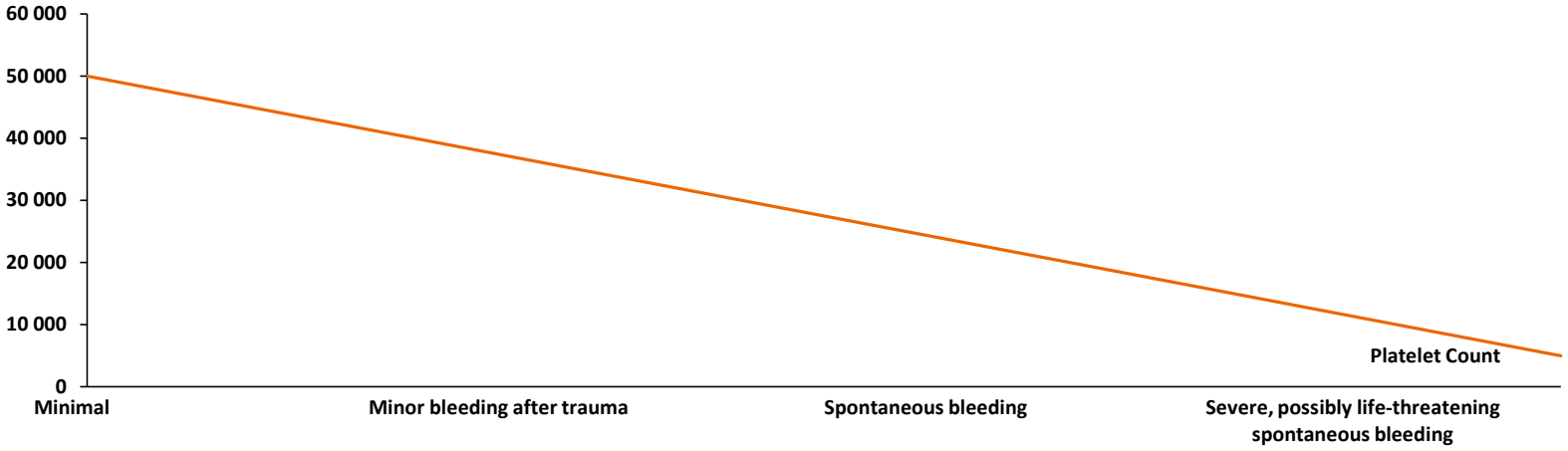


1. Scharf RE. Acquired platelet function disorders: pathogenesis, classification, frequency, diagnosis, clinical management. Hämostaseologie. 2008;28:299-311.
2. Guillaume M, et al. Prevalence of thrombocytopenia and thrombocytosis upon acute hospital admission to internal medicine units. A cross-sectional study in Denmark. European Journal of Inner Medicine. 57:e34-e37.

Relation of platelet count and bleeding risk

Platelet Count	Risk of Bleeding
≥50,000/µL	Minimal
20,000–50,000/µL	Minor bleeding after trauma
<20,000/µL	Spontaneous bleeding
<5000/µL	Severe, possibly life-threatening spontaneous bleeding

→ **Reduced platelet function (e.g., due to uremia or aspirin use) adds risk of bleeding in each platelet count range.**



Suspect a bleeding disorder?

As a possible diagnostic strategy, ask these important questions:

Is it pathological bleeding, or is the bleeding within the upper normal range?

Is the bleeding due to a congenital/familial or acquired disorder?

Which part of blood coagulation is affected: primary hemostasis (platelet or blood vessel wall problem) or secondary hemostasis (coagulation problem)?

Does the patient have a systemic disease that could cause or exacerbate the bleeding?

Does the patient take any medication that might exacerbate the bleeding tendency?

Steps in bleeding risk screening

Bleeding signs, bleeding history, family history for bleeding, prior to high-risk surgery, or other risk factors

PT, APTT, fibrinogen, platelet count, PFA testing

normal

- No further testing; therapy on standby

abnormal

- Exclusion of anticoagulation therapy
- Determination single factors
- VWF testing

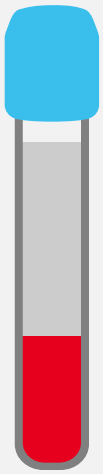
Testing for platelet disorders

Platelet testing scenario

Bleeding risk management

Antiplatelet drug-therapy management

Thrombophilia and risk factors



Standard platelet functionality tests (e.g., INNOVANCE® PFA-200 System*)

Positive

Uncertain

Negative

Platelet aggregation testing

University and central hospital labs, specialty labs, research labs

Multiplate System

VERIFYNOW System

Helena AGGRAM System

CHRONO-LOG System

*Not available for sale in the U.S. Product availability varies by country.

Different methodologies for assessment of platelet function

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Bleeding time	Tests based on platelet aggregation under shear stress	Tests based on platelet aggregation	Platelet function methods combined with viscoelastic test
IVY method	INNOVANCE PFA-200*	Light transmission platelet aggregation (LTA)	TEG PLATELET MAPPING systems
Duke method	Impact [cone and platelet analyzer]	Impedance aggregation	ROTEM platelets
	Global Thrombosis Test (GTT)	Lumiaggregometry platelet works	

Uses platelet-rich plasma

Uses whole blood

*Not available for sale in the U.S. Product availability varies by country.
Note: Flow cytometry and thrombaxane metabolites are not listed here.

What‘s behind light transmission aggregometry (LTA)?

Light transmission aggregation: a look back

Gustav Victor Rudolf Born

Born 29 July 1921 in Göttingen

Died 16 April 2018

Gold standard

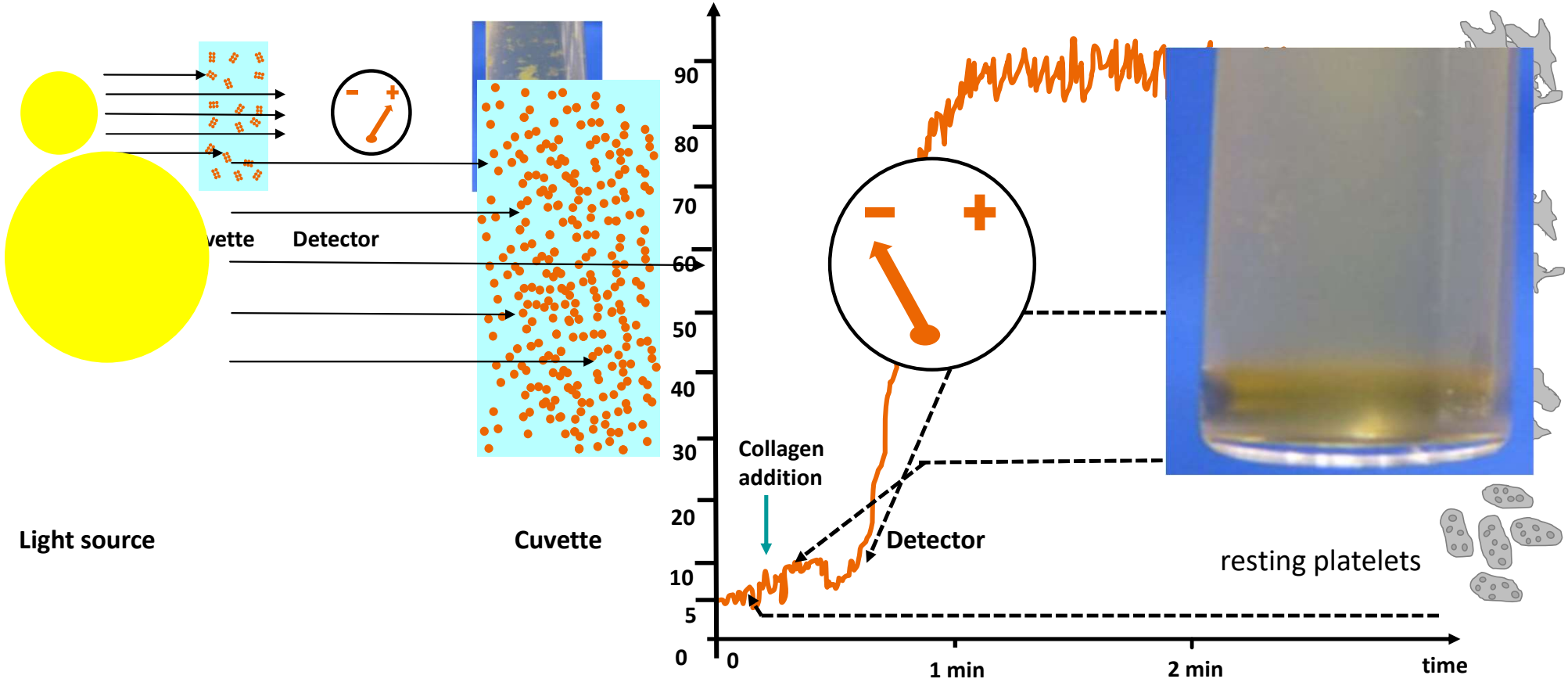
in platelet function testing

>3300 articles

on light transmission aggregation (LTA)

in PubMed

Light transmission aggregation measurement principle



Source for pictures: Thomas Scholz [2018].

Which reagent is used for which testing purpose?

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Differential aggregation responses in patients with thrombocytopathies

Syndrome	ADP	Collagen	Arachidonic acid	Ristocetin
Glanzmann thrombasthenia	▼- Ø	▼- Ø	▼- Ø	n - ▼
Bernard-Soulier syndrome	n	n	n	▼- Ø
May-Hegglin syndrome	n - (▼)	n	?	n
δ-Storage pool disease	n - ▼	▼	n - ▼	n - ▼
α-Storage pool disease	n - ▼	▼	n	n
Aspirin-like defect	▼	▼	▼	n

n = Normal; Ø = absent; ▼= inhibited or reduced; (▼) = slightly inhibited.

Disclaimer: When a pathological value is measured in some of the screening tests, further investigations are necessary because different platelet functions (e.g., primary activation, adhesion and aggregation capability, platelet secretion, and procoagulant activity of platelets) may be affected in thrombocytopathy.

Source: Kirchmaier, et al. Transfus Med Hemother. 2010 Oct;37(5):237-46.

Available guidelines for platelet aggregation

1. CLSI. Platelet function testing by aggregometry; approved guideline. CLSI document H58-A. Wayne, PA: Clinical Laboratory Standards Institute; 2008. **[CLSI Guideline]**

2. Cattaneo M, Cerletti C, Harrison P, Hayward CPM, Kenny D, Nugent D, Nurden P, Rao AK, Schmaier AH, Watson SP, Lussana F, Pugliano MT, Michelson AD. Recommendations for the standardization of light transmission aggregometry: a consensus of the working party from the platelet physiology subcommittee of SSC/ISTH. J Thromb Haemost. 2013;11: 1183-9. **[SSC Guideline]**

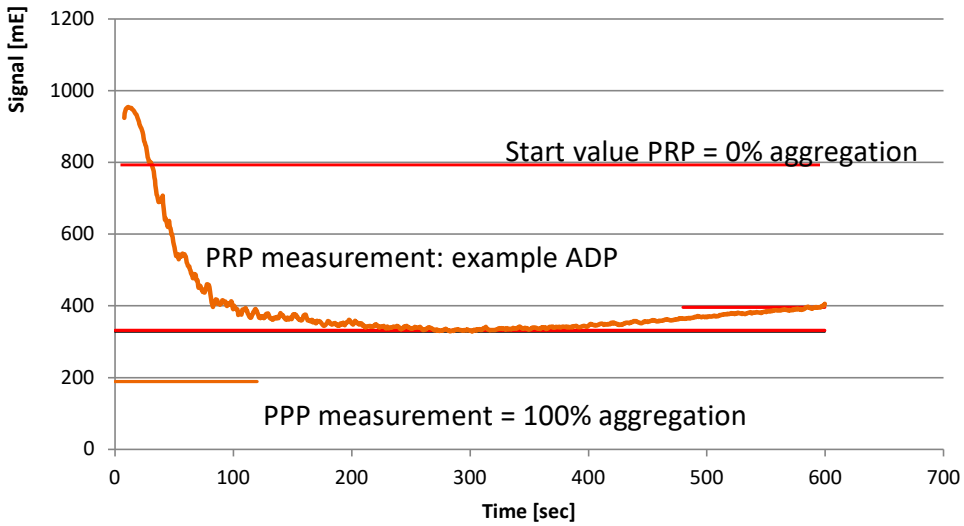
3. Gesellschaft für Thrombose- und Hämostaseforschung (GTH e.V.): Diagnose von Thrombozytenfunktionsstörungen – Thrombozytopathien, AWMF-S2k-Leitlinie 086-003, 2018. (Available in German language only.) **[GTH Guideline]**

Recommended concentrations according to different guidelines

	ADP	ARA	COL	EPI	RIS
SSC 2013	2 µM	1 mM	2 µg/mL	5 µM	1.2 mg/mL / 0.5–0.7 mg/mL
CLSI H58-A	5 µM	0.5–1.6 mM	2 µg/mL	5 µM	0.8–1.5 mg/mL / ≤0.6 mg/mL
German guideline on thrombocytopathies	2–3 µM*	1–1.5 mM	0.5–2 µg/mL	5 µM	1.2–1.5 mg/mL / 0.5–0.6 mg/mL
Atellica® COAG 360 System†	5 µM	1 mM	2 µg/mL	5 µM	1.2 mg/mL / 0.5 mg/mL

*ADP 2–3 µM: Use double concentration if no reaction with low concentration. Evaluation of "second wave": A sample should aggregate while using 2–3 µM ADP. After holding time, samples require higher concentrations: increase to 4 µM.
† Not available for sale in the U.S. Product availability varies by country.

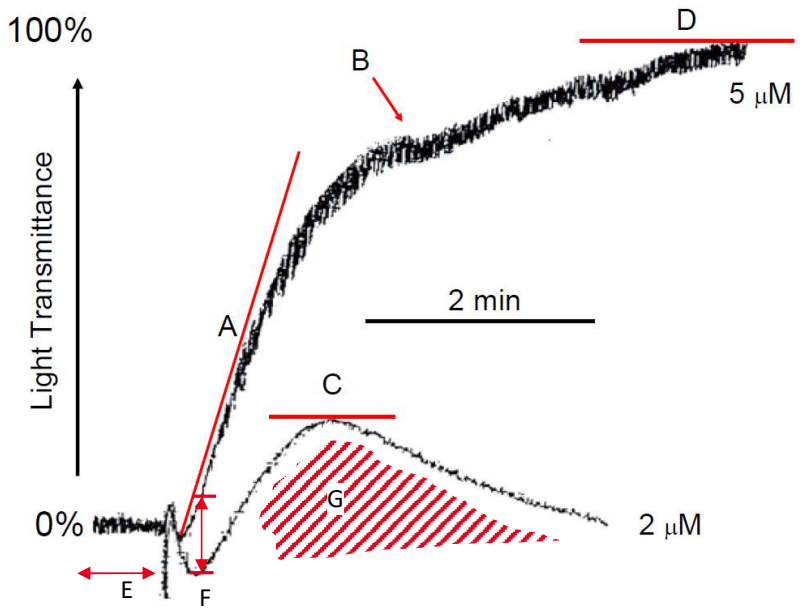
Result reporting: percent aggregation curve



Percentage aggregation (t) =

$$\frac{\text{Start value PRP} - \text{measurement PRP (t)}}{\text{Start value PRP} - \text{PPP value}}$$

Available evaluations for the characterization of the aggregation curve



Result interpretation according to CLSI/ISTH[1]

Slope (A), evtl. 2. Slope (A')
Raw value method: Vmax abs, Vmax second wave

Minimum conc. needed to induce secondary wave ADP, EPI (B)
Raw value method: second wave?

Percent maximum aggregation (C)
Raw value method: maximum aggregation

Percent final aggregation (D), disaggregation (C–D)
Raw value method: end aggregation, disaggregation

Lag phase (E)
Raw value method: lag time

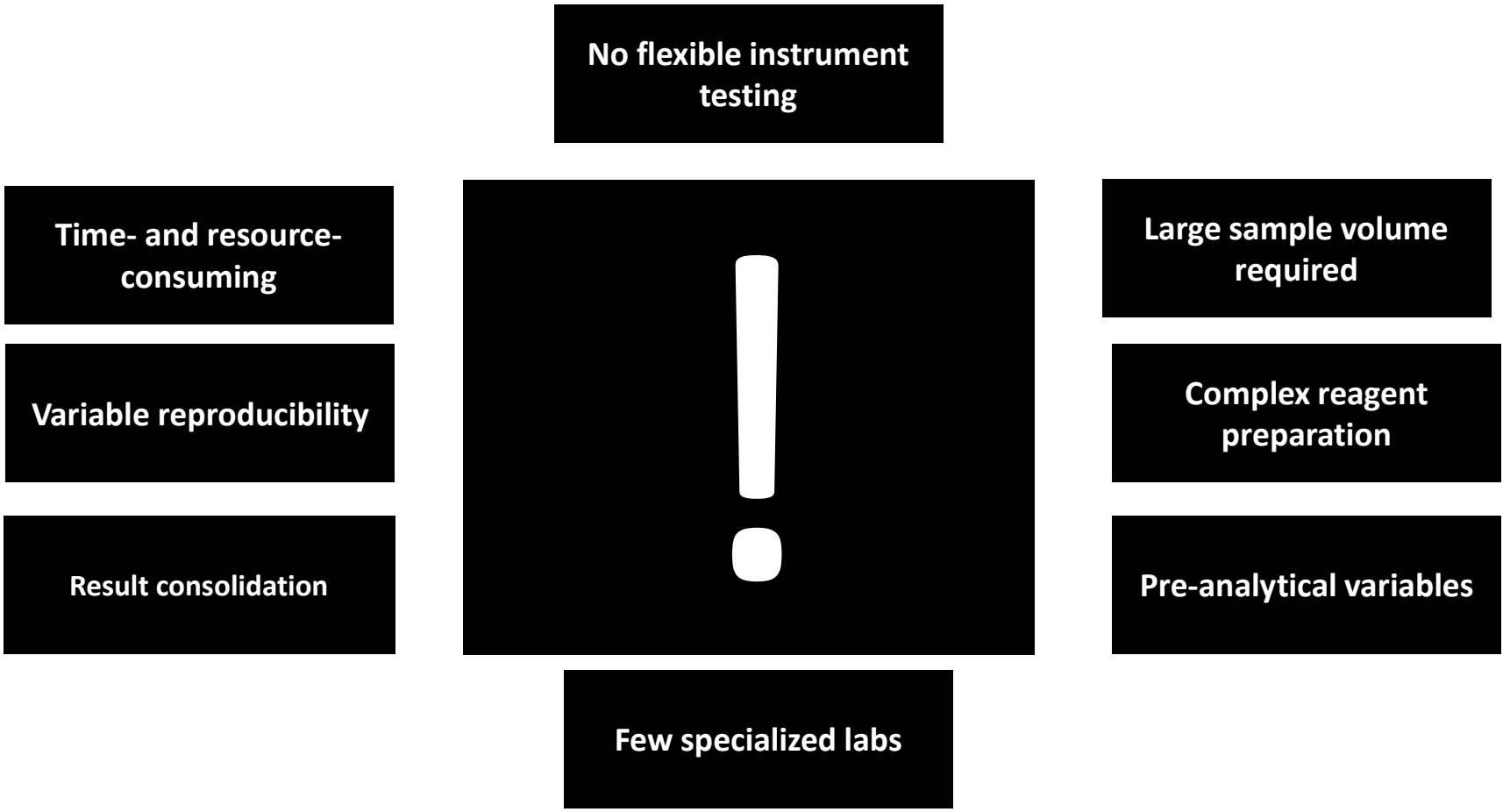
Shape change (F)
Raw value method: shape change

Area under the curve (AUC) (G)
Raw value method: AUC

1. CLSI. Platelet function testing by aggregometry; approved guideline. CLSI document H58-A. Wayne, PA: Clinical Laboratory Standards Institute; 2008.

What makes platelet testing challenging?

Challenges in platelet aggregation testing



"The ideal test of platelet function for use in clinical practice would ***be rapid, easy-to-use, inexpensive, and would be a reliable indicator of the clinical response to the specific antiplatelet therapy*** *or combination of therapies."*

Braunwald E, Angiolillo D, et al. Assessing the current role of platelet function testing. Clin. Cardiol. 2008 Mar;31(3 Suppl. 1):I10-I16.

How do Siemens Healthineers integrated platelet aggregation testing solutions overcome these challenges?

Siemens Healthineers and Sysmex integrate platelet aggregation onto routine and specialty hemostasis analyzers

Atellica COAG 360 System is not available for sale in the U.S. Product availability varies by country.

Comprehensive family of systems for platelet aggregation testing

Hemostasis Portfolio			Clotting	Chromogenic	Immunologic	Platelet Aggregation	PSI™ Checks	Automation Connectivity	High-sensitive Immunoassay
High Volume ↑	Atellica® COAG 360 System*		•	•	•	•	•	•	•
	Sysmex® CS-5100 System		•	•	•	•†	•	•	
	Sysmex CS-2500 System		•	•	•	•†	•		

* Not available for sale in the U.S. Product availability varies by country.
†HYPHEN BioMed CE-marked application. Not available for sale in the U.S. Product availability may vary from country to country and is subject to varying regulatory requirements.

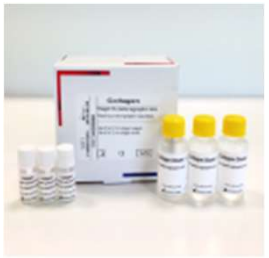
Atellica COAG 360 System*: no more gaps in platelet aggregation testing

Siemens Healthineers platelet aggregation testing solutions can test for five agonists

- HYPHEN BioMed-labeled reagents*
- CE-marked application† and IVDR-conforming
- Available OUS, as RUO in U.S.
- Reagents distributed by Siemens Healthineers and HYPHEN BioMed

Seven Days
7-day dilution of agonists by system and 7-day onboard stability ‡


Ristocetin*


Collagen*,§


Epinephrine*


ADP *


Arachidonic Acid *

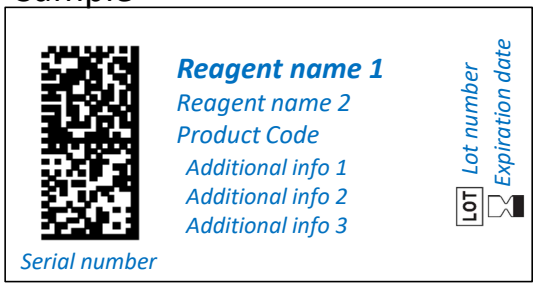
* Not available for sale in the U.S. Product availability varies by countries.
† Siemens Healthineers CE-marked applications for Atellica COAG 360 System. Not available for sale in the U.S.
‡ For epinephrine, collagen, and ristocetin.
§ Collagen source: equine reconsitiuted in acid buffer.

Intelligent sample and reagent management helps to simplify platelet aggregation testing

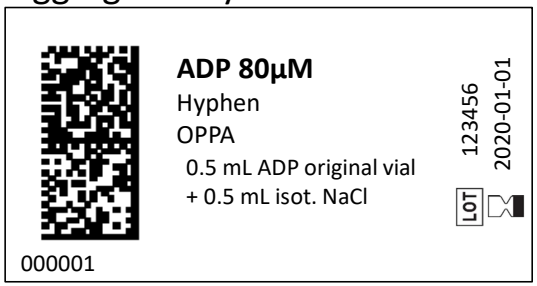
Atellica COAG 360 System* allows printing of 2D bar codes for reagents.

- The bar-code label enables the system to automatically identify reagent.
- A unique vial number for each reagent ensures monitoring of onboard stability.
- Bar-code maker facilitates the process of final reagent preparation.
- Bar-code labeling can be used for any other reagent.

Sample



Aggregometry



For further instructions, see operator's manual.

*Not available for sale in the U.S. Product availability varies by country.

Available applications for platelet aggregation testing

Siemens Healthineers CE-marked applications

Six CE-marked applications for five different agonists*

- ADP 5 µM
- Epinephrine 5 µM
- Arachidonic acid 1 mM
- Ristocetin 1.2 mg/mL and 0.5 mg/mL
- Collagen 2 µg/mL

Eight additional applications†

- ADP 10 µM, 2 µM, 1µM
- Epinephrine 10 µM, 2 µM, 1 µM
- Collagen 10 µM
- TRAP 1 µM

140 µL PRP

System requires up to 44% less sample volume than traditional manual methods

*Applications were validated (performance data and application instructions available).
†Without performance data, e.g., reference range.
Atellica COAG 360 System is not available for sale in the U.S.

Improved sample management for platelet aggregation

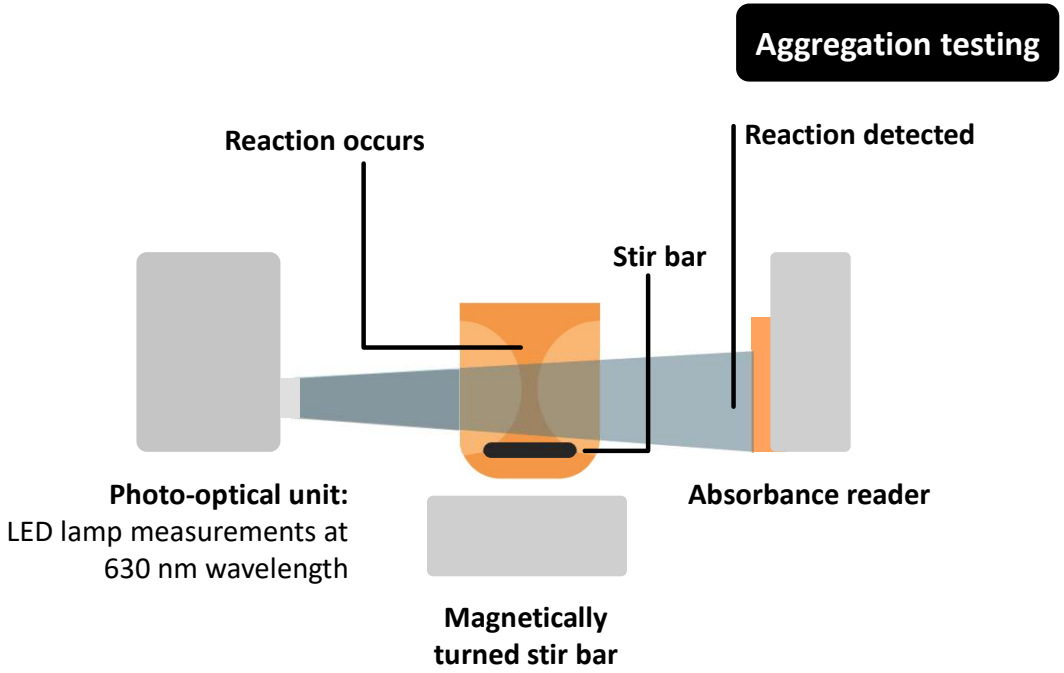
- Flexible rack configurations: plasma type (PRP/PPP) identified via defined rack
- PPP sample can be run from routine samples
- Advanced pre-analytical sample quality (PSI) checks for PPP samples
- HIL* indices are assigned to the respective aggregation measurement results
- Continuous loading

Three pre-analytical indices
Intelligently identify HIL-affected samples to reduce pre-analytical variables

*HIL: hemolysis, icterus, lipemia
Atellica COAG 360 System is not available for sale in the U.S. Product availability varies by country.

Automated reaction stirring supports more-reliable results in aggregation testing

One standardized process
Automated process streamlines workflow



Four testing channels available on the Atellica COAG 360 System*

*Not available for sale in the U.S. Product availability varies by country.

Integrated platelet aggregation on Atellica COAG 360 System*

Three manual steps
Operations can be reduced to only three manual steps

Atellica COAG 360 System*

*Not available for sale in the U.S. Product availability varies by country.

Atellica COAG 360 System* supports accelerated throughput for platelet aggregation testing

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Profile 1: Aggregation only	
PRP samples	●●●●●
Agonists	★★★★★
Applications	■■■■■

1 h:25 min
29 PRP samples/h

Profile 2: Typical special hemostasis profile† + aggregation	
Total number of patient samples: 100	
PRP samples	●●●●●
Agonists PRP 1,3,5	★★★★☆
Applications PRP 1,3,5	■■■■□□
Agonists PRP 2,4	★★★★★
Applications PRP 2,4	■■■■■■

2 h:50 min
151 samples/h

*Not available for sale in the U.S. Product availability varies by country.
†PT, aPTT, Fibrinogen, Thrombin, Thrombin Time, INNOVANCE® Antithrombin, INNOVANCE D-Dimer, Protein C, INNOVANCE Free PS Ag, Actin® FS Factor VIII

Atellica COAG 360 System* supports accelerated throughput for platelet aggregation testing

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Profile 3: Typical special hemostasis profile† + aggregation

Total number of patient samples: 100

PRP samples	●●○○○
Agonists PRP 1	★★★★☆
Applications PRP 1	■■■■□□
Agonists PRP 2	★★★★★
Applications PRP 2	■■■■■■

2 h:24 min
163 samples/h

Profile 4: Typical special hemostasis profile† + aggregation as STAT

Total number of patient samples: 100

PRP samples	●●○○○
Agonists PRP 1	★★★★☆
Applications PRP 1	■■■■□□
Agonists PRP 2	★★★★★
Applications PRP 2	■■■■■■

2 h:06 min
189 samples/h

*Not available for sale in the U.S. Product availability varies by country.
†PT, aPTT, Fibrinogen, Thrombin, Thrombin Time, INNOVANCE Antithrombin, INNOVANCE D-Dimer, Protein C, INNOVANCE Free PS Ag, Actin FS Factor VIII

Atellica COAG 360 System* enables thorough traceability of platelet aggregation results

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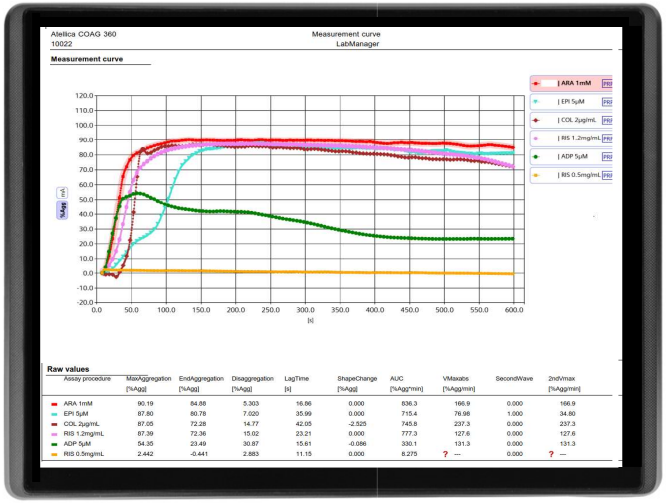
Traceability of results

- Atellica COAG 360 System provides all nine different evaluation parameters for the characterization of the aggregation curve (see slide 18).
- All nine curve parameters can be transferred to the LIS, giving you in-depth audit and archive capabilities.
- Aggregation curve is displayed with customized color coding and comment field.
- Aggregation curves can be printed or exported as PDF via USB,† supporting a paperless working environment.

One source
All hemostasis test results come from one source/system



*Not available for sale in the U.S. Product availability varies by country.
† Transfer of PDF files to LIS in development.

What are the advantages for your laboratory?

Siemens Healthineers makes platelet aggregation more manageable, reliable, and accessible

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- Time- and resource-consuming testing
- No flexible instrument testing
- Complex reagent preparation
- Variable reproducibility
- Large sample volume required
- Result consolidation
- Few specialized labs
- Pre-analytical variables

*For epinephrine, collagen, and ristocetin.
Atellica COAG 360 System is not available for sale in the U.S.
Product availability varies by country.

Rethink platelet aggregation!
Thank you.

SIEMENS Healthineers

Transforming care delivery through improved access to care.