

Managing Variation in Response to Clopidogrel

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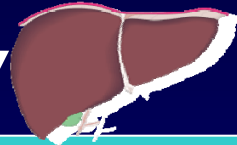
Disclosures: Dr. Antman is a member of the TIMI Study Group that receives grant support from Eli Lilly, BMS-Sanofi, and Daiichi-Sankyo

Variation in Response to Clopidogrel: Potential Sites



Intestinal absorption

85% Inactive
Metabolites
Esterases



Hepatic metabolism
Cytochrome P450 pathway

**Genetic variations
in ability to form
active metabolite**

Active metabolite

P2Y₁₂ receptor
(irreversible inhibition)

VASP ASSAY

Inadequate administration

Poor compliance

← Variable absorption

Drug-drug interactions

← CYP polymorphisms

Drug-drug interactions

P2Y₁₂ receptor polymorphisms

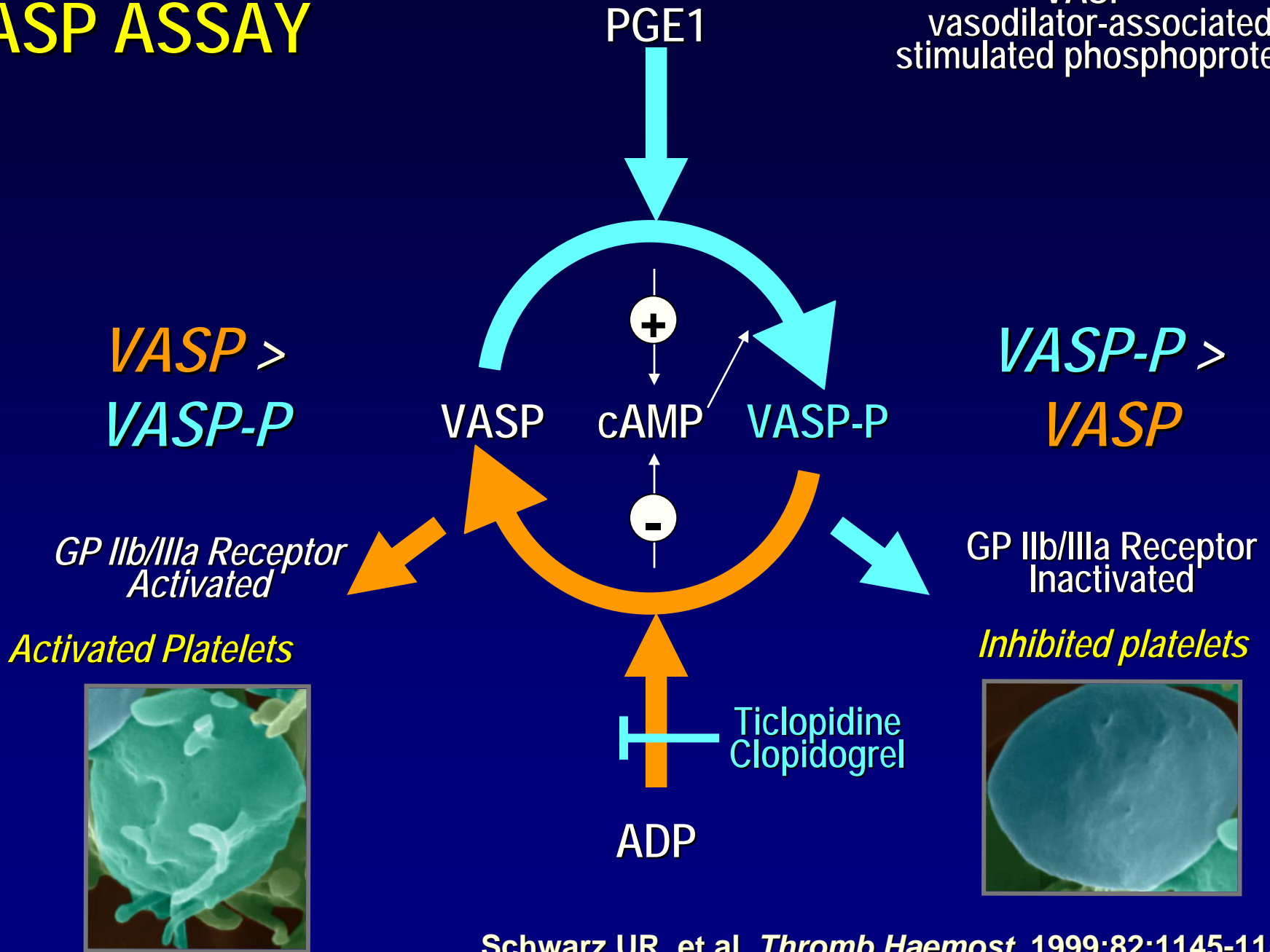
Alternate pathways of
plt activation

← ↑ release of circulating ADP

Higher baseline
platelet reactivity

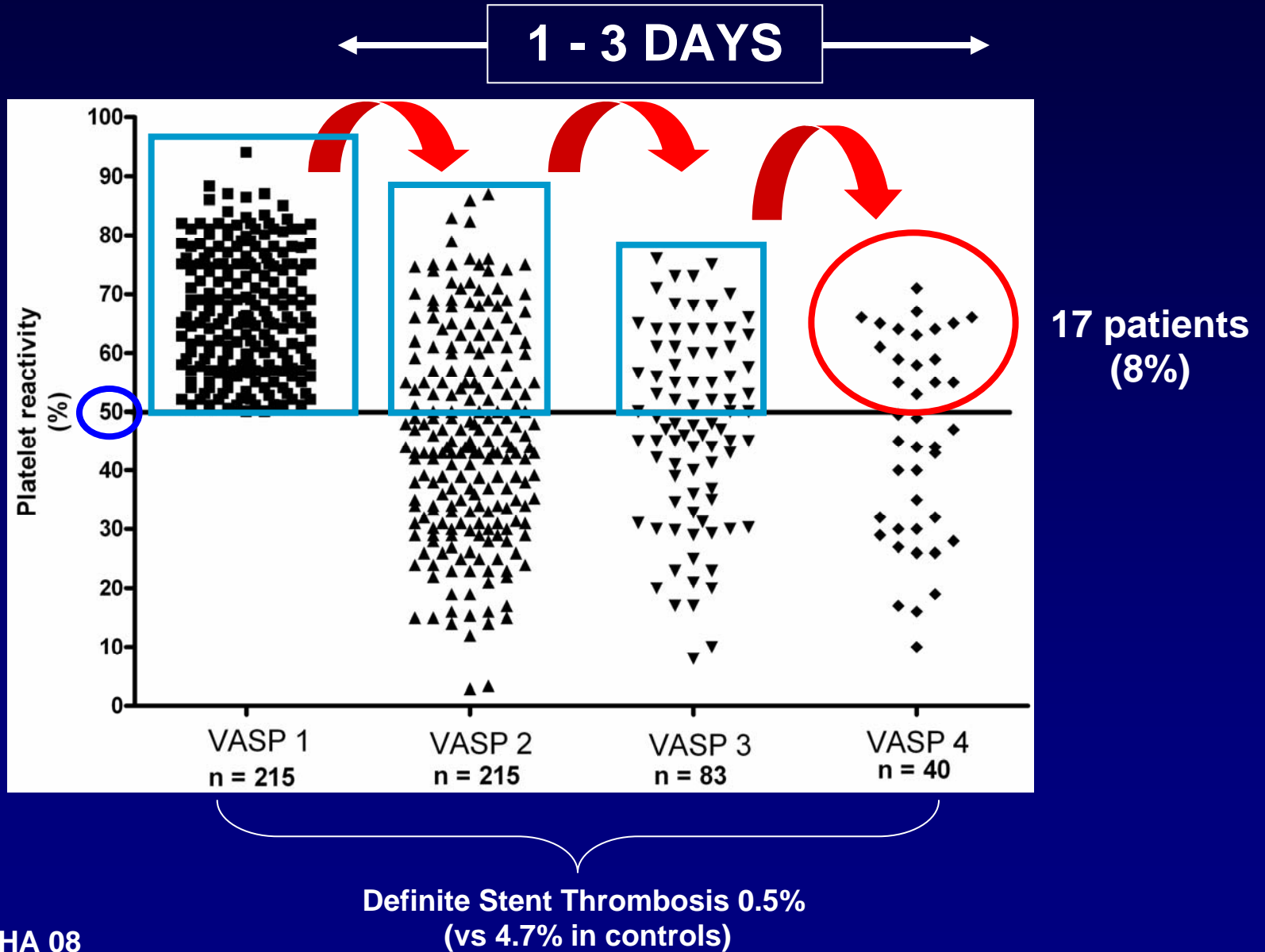
VASP ASSAY

VASP =
vasodilator-associated
stimulated phosphoprotein



Schwarz UR, et al. *Thromb Haemost.* 1999;82:1145-1152.
Geiger J, et al. *Arterioscler Thromb Vasc Biol.* 1999;19:2007-2011.

VASP Reactivity Monitoring



Variation in Response to P2Y12 Inhibition

Treatment Failure

Complex Biologic Process

Poor Compliance

Resistance to Treatment

Empiric Increase in Dose

OASIS 7

High vs STD dose Clopidogrel -- PCI

Inadequate Response: Lab Test

1. *Correlation w Outcomes*
2. *Captures Rx Effect Completely*
3. *Reproducible across therapies in class*

GRAVITAS

Tailored vs STD Clopidogrel post PCI

Inadequate Biologic Response

Alternatives to Lab-Guided Clopidogrel Dosing for P2Y12 Inhibition

Thienopyridine

Prasugrel

Higher levels of Active Metab.
Greater IPA
(vs STD and Hi Dose Clopidogrel)

<u>Event</u>	<u>% Decr</u>
CVD/MI/Stroke	19
MI	24
Stent Thromb	52

Increased Bleeding
*PK/PD Model: Reduce Dose
if < 60 kg or \geq 75 yrs*

Non-thienopyridine

AZD 6140 (PLATO)

Cangrelor (CHAMPION)