Optimizing Antiplatelet Use from a Dissolution Study of Antiplatelet Products Marketed in Indonesia

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Outline

- Antiplatelet agents & use
- Antiplatelet effects of ASA
- Enteric-coated low-dose ASA
  - Daily low-dose ASA
  - Rationale for enteric-coated ASA
- Dissolution test
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- Results
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  - Dissolution profiles in buffer stage
  - Free salicylic acid
- Conclusions

Various antiplatelet agents

- Aspirin
- P2Y12 receptor antagonists:
  - clopidogrel (Plavix(R))
  - ticlopidine (Ticlid(R))
  - ticagrelor (Brilinta(R))
- Phosphodiesterase inhibitors :
  - dipyridamole (Persantine(R))
  - cilostazol (Pletaal(R))
- Glycoprotein IIb / IIIa receptor antagonists :
  - abciximab (Reopro(R))
  - eptifibatide (Integrilin(R))
  - tirofiban (Aggrastat(R))

Antiplatelet Use from various Guidelines :

1ry prevention: not recommended in Indonesia

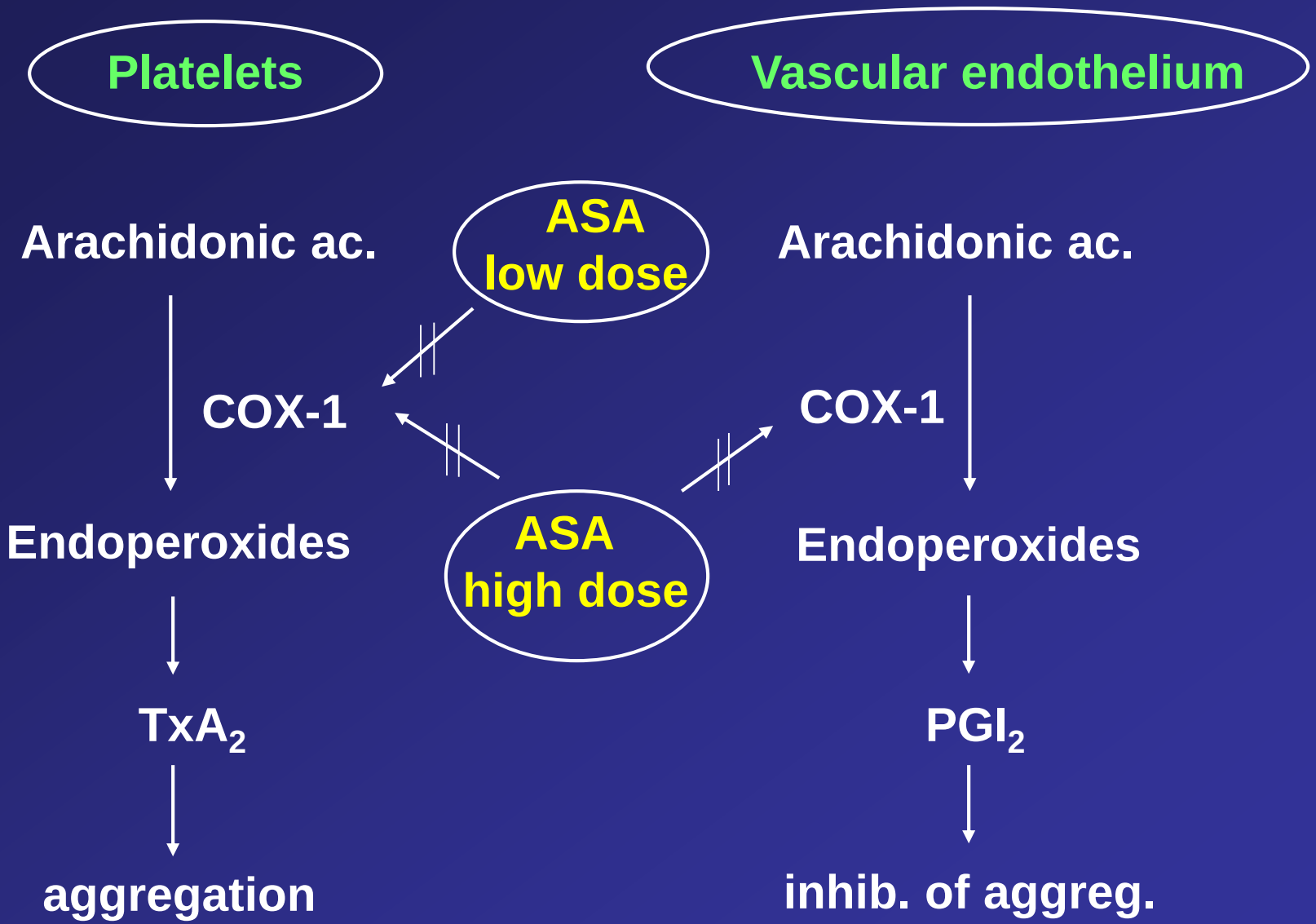
2ry prevention:

- Ischemic Stroke & TIA (Transient Ischemic Attack)
- ACS (Acute Coronary Syndrome)
- STEMI (ST-elevated Myocardial Infarction)
- NSTEMI (Non ST-elevated Myocardial Infarction)
- UA (Unstable Angina)
- CABG & PCI with stent

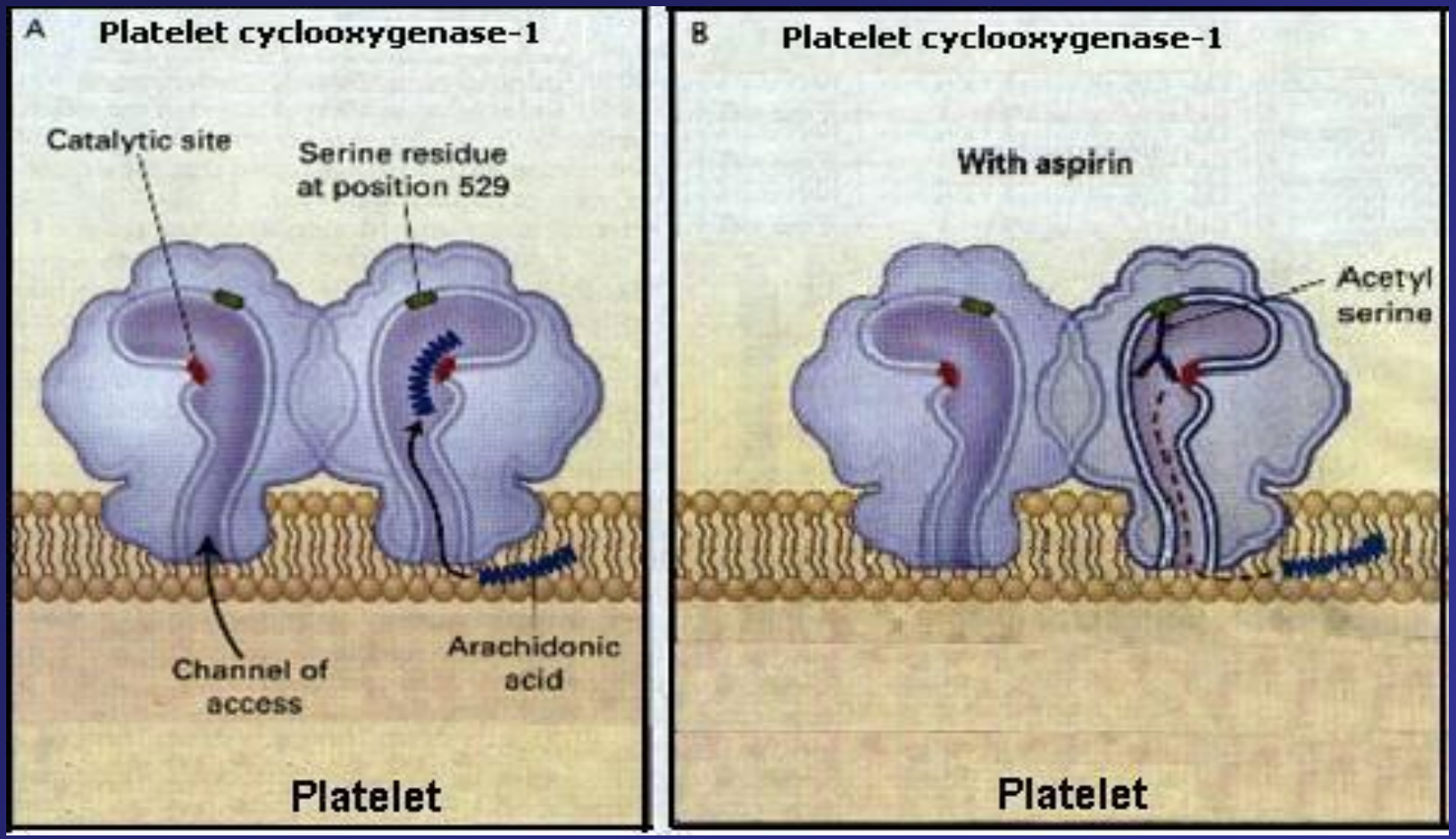
Antiplatelet of choice / 1st line: low-dose Aspirin

The antiplatelet effects of Aspirin

Inhibition of COX-1 by ASA (1)



Mechanism of action of ASA



COX-1 active site is a long hydrophobic channel, and arachidonic acid substrate gains access to the active site from the interior of the membrane bilayer.

ASA acetylates Ser 529 at the apex of the long active site

→ blocks access of arachidonic acid to the active site

→ inhibits COX-1 irreversibly

(Catella - Lawson et al, 2001)

Inhibition of COX-1 by ASA (2)

Irreversible inhibition of COX-1 by ASA →

- **in platelets : no nucleus → no synth. of new proteins → the action of ASA is permanent, lasting for the life of the platelets (8-10 days)**
- **in vascular endothelial cells : have nucleus → new COX is produced constantly → the action of ASA is not permanent**

Inhibition of COX by ASA

ASA : much less active against COX-2 than COX-1
(selectivity towards COX-1 150 x)

In stomach mucosa : PGs (PGI_2 & PGE_2) are cytoprotective

↓

inhib. of synth. by ASA causes
gastric damage & bleeding

Patrono, 1994

Effects of ASA in platelets

- Clinically relevant inhibition of platelet function requires practically complete (80-90 %) inhib. of TxA_2 synth.

- ~ 10 - 20 % intact platelets is required for normal hemostatic function

  ~ 10 % of circulating platelets is replaced every 24 hrs

  → platelet aggreg. requires 48 hrs to recover

  → sufficient to discontinue use of ASA 48 hrs before planned operation

Note : In vascular endothelium :
inhib. of vascular COX by ASA requires 3-6 hrs to recover

Pharmacokinetics of low-dose ASA (1)

- **Oral ingestion → rapid absorption from GI tract**

  - **into the presyst. portal circulation.**
    There, ASA meets platelets &
    irreversibly inactivates their COX-1
    ↓
    the platelets become impotent in prod. TxA_2 for the rest of its life of 8-10 days in the circulation

  - **enters the liver → 60 % deacetylated →**

  - **the remaining ASA mols enter systemic circulation, reach peak within 20 min, mix with venous blood → conc. of ASA in systemic circul. is very much lower → inhib. of PGs production in endoth. cells & stomach mucosa is preferentially spared**

Vane & Meade, 1997

Pharmacokinetics of low-dose ASA (2)

- Esterases are present in the GI mucosa, plasma, and liver → hydrolyze ASA to salicylic acid & acetic acid

- ASA is completely absorbed from GI tract, then ASA is rapidly hydrolyzed to salicylic acid with a half-life of ~ 15 min. → plasma levels of ASA are undetectable 1-2 hrs after dosing.

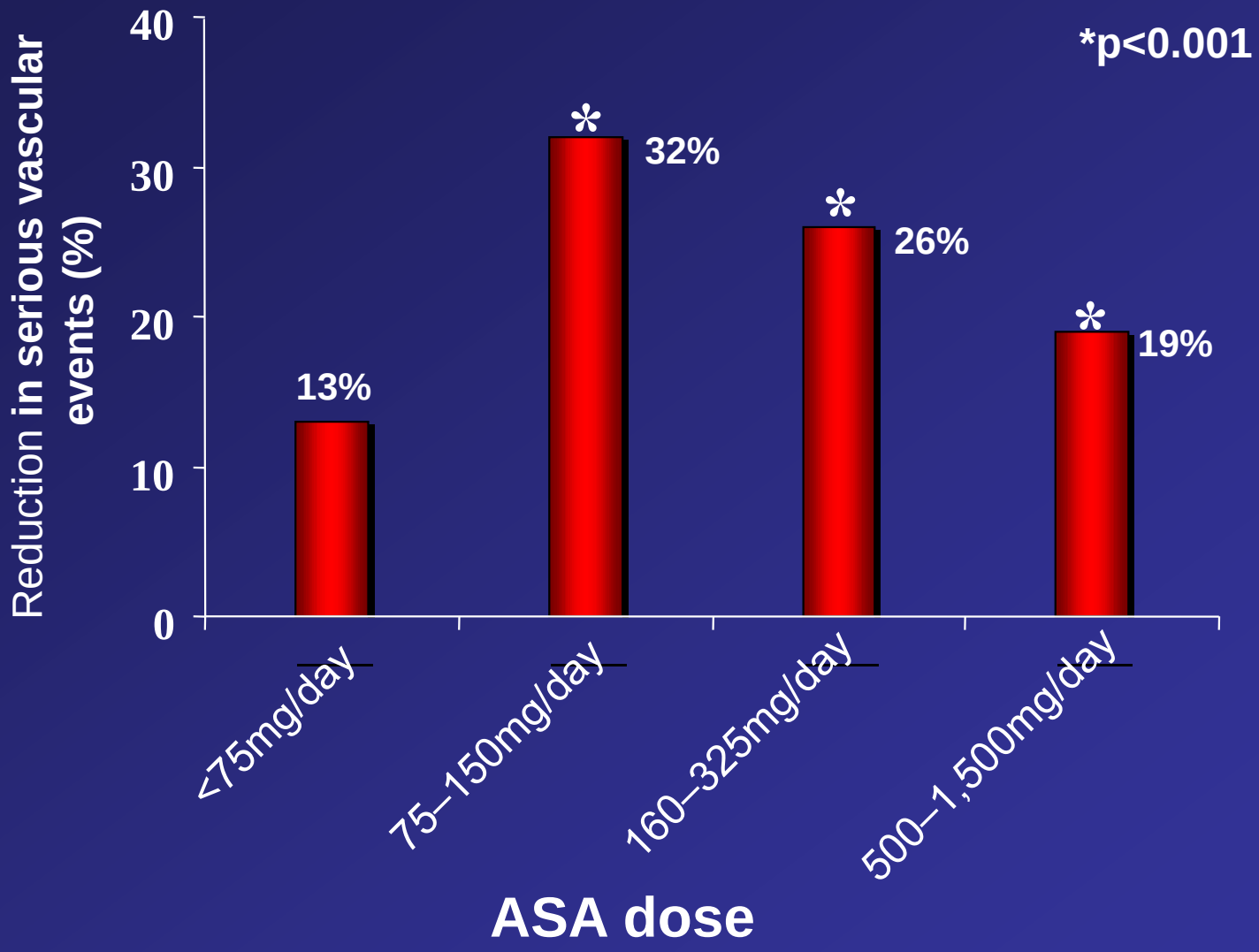
Action of low-dose ASA as antiplatelet

- acetylation of platelet COX-1 by low-dose ASA mostly occurs in portal circulation before ASA is deacetylated to salicylic acid (mostly in the liver)

  ↓

  portal circulation is the most important site of action of ASA as an antiplatelet agent

Daily low dose ASA :



(Antithrombotic Trialists Collaboration.BMJ 2002;324:71-86)

Frequency & time of adm. of ASA as antiplatelet

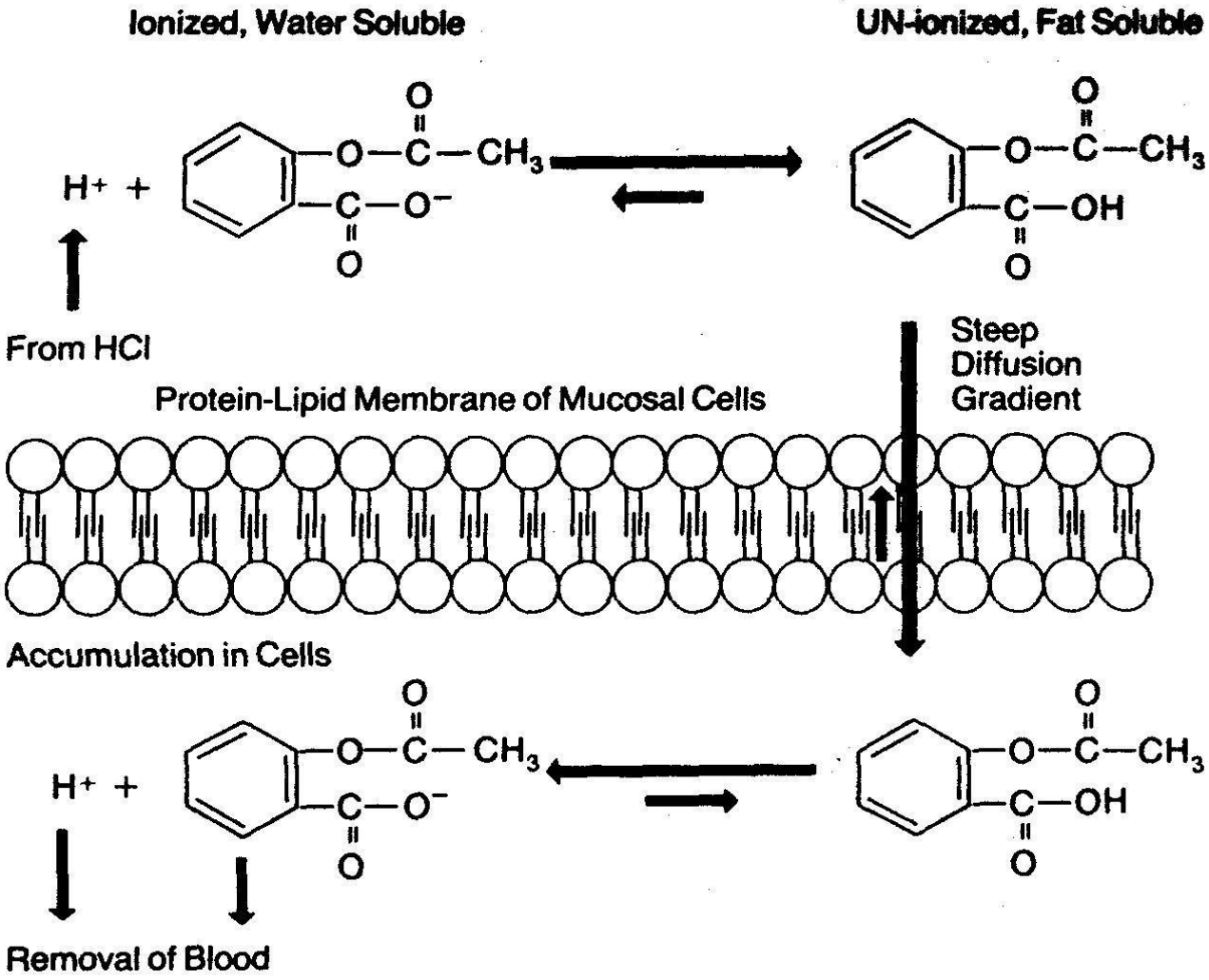
- Freq. small doses → ↑ tolerability
  ↓ undesired PGs inhibition
  but for compliance → once daily

- Time of administration : in the afternoon
  - platelet count higher in the afternoon
  - in high-risk groups, evening adm. → ↓ BP
  - morning adm. : more rapid excretion

- With regard to meals :
  - conventional tablet : after meals
  - enteric-coated tablet : any time

Rationale for enteric-coated ASA (1)

ASA-induced gastric damage (1)



Gastric lumen : pH ~ 1.5

ASA : pKa = 3.5

unionized in gastric lumen ~ 99%

↓

diffuse across gastric epith. membrane

↓

Gastric epith. cell : pH ~ 7

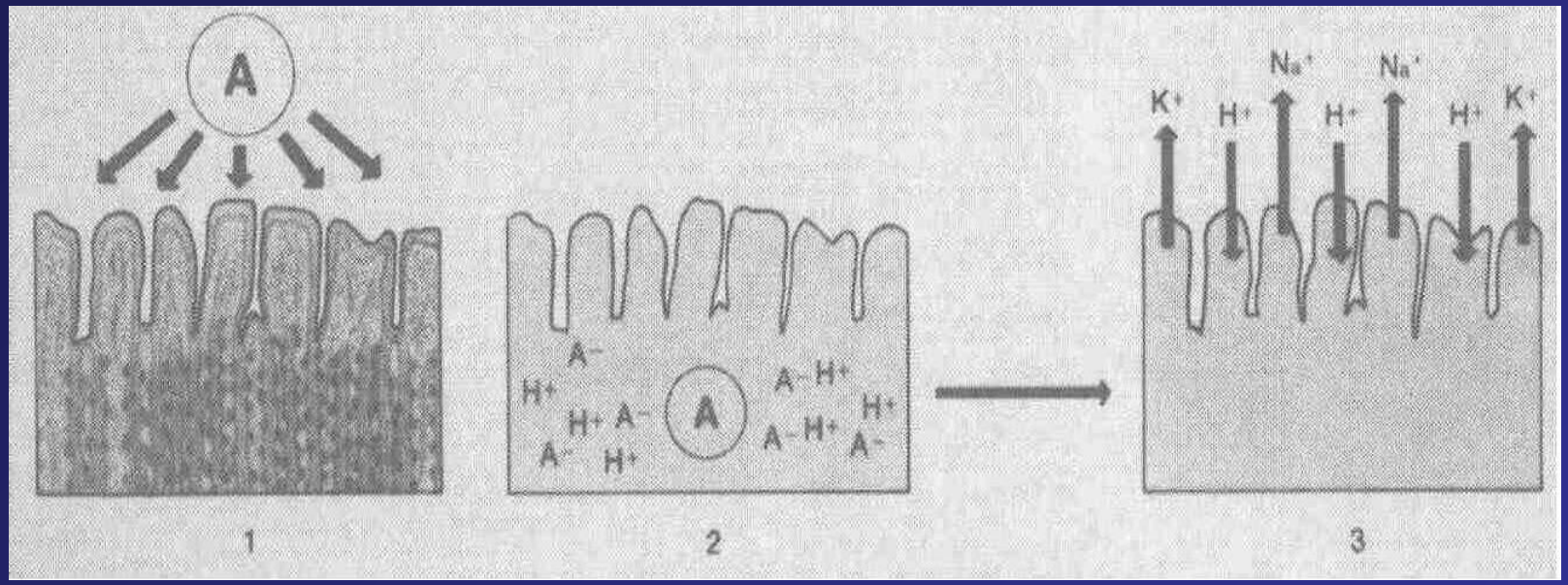
ionized in gastric epith. cells ~ 99.7 %

(ion trapping)

(Schoen & Vender, 1989)

Rationale for enteric-coated ASA (2)

ASA-induced gastric damage (2)



ASA enters gastric epith. cells → ionized & entrapment

↓

↑ permeability of cell membrane to H^+

↓

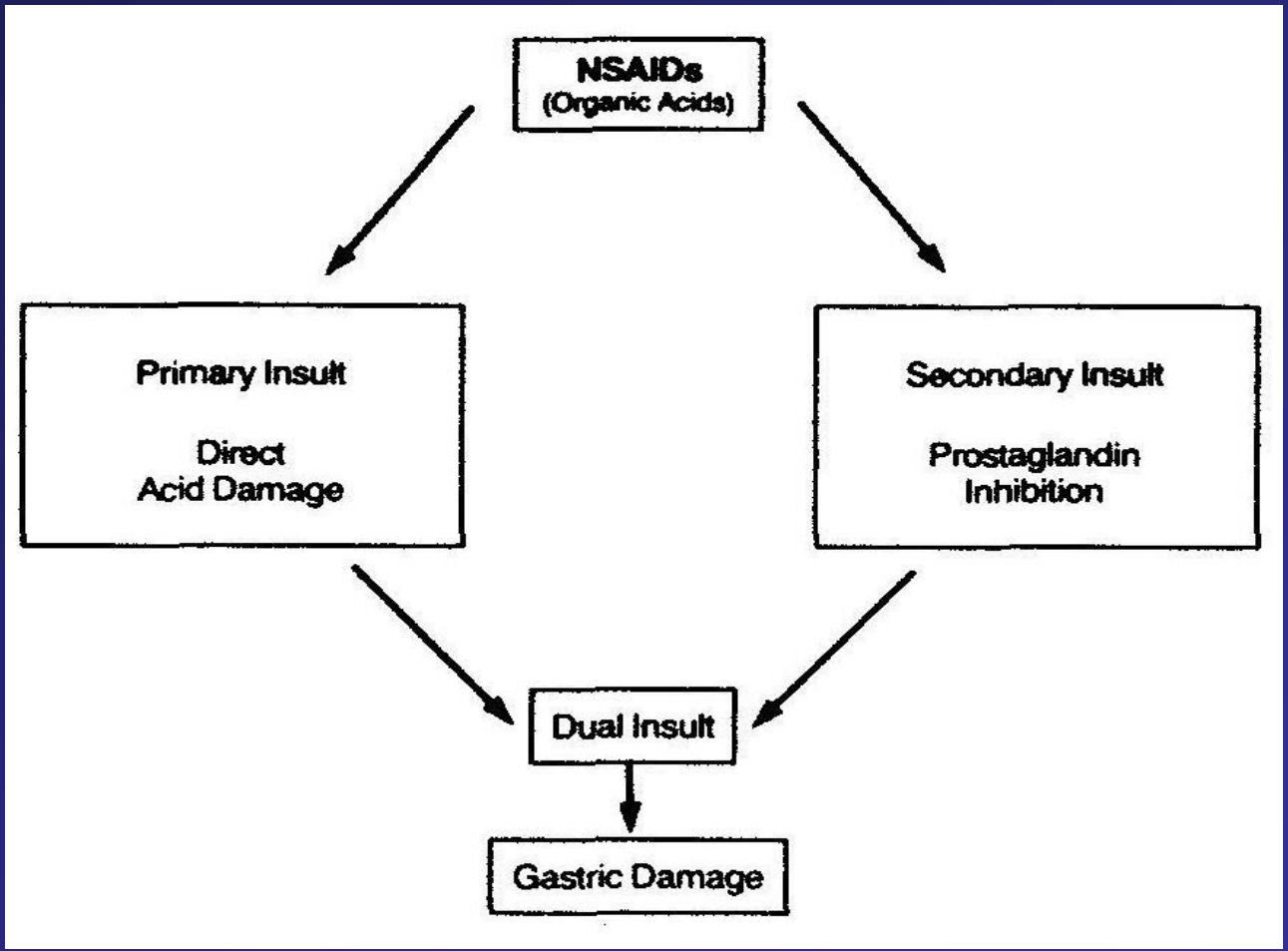
back diffusion of H^+ from gastric lumen

↓

gastric damage
(erosion & bleeding)

(Schoen & Vender, 1989)

ASA-induced gastric damage (3)



Schoen & Vender, 1989

Both insults are necessary :

first, direct acidic damage, followed by inhibition of "cytoprotective" PGs synthesis (↓ gastric ac. secretion, ↑ gastric mucosal blood flow & hydrophobicity, ↑ mucus & bicarbonate secretion)

Rationale for enteric-coated ASA (4)

Gastroduodenal tolerability of low-dose ASA

To reduce gastric damage :

avoid both insults, esp. the primary insult :

avoid the direct contact between ASA & the gastric mucosal cells

↓

by formulating ASA in enteric-coated tablet

Enteric-coated ASA tablets are designed to disintegrate in the small intestine at a pH of 6-7

(bypass the stomach (pH ~ 1.5) & duodenum (pH 2-4))

↓

ASA dissolves completely & > 99% in the ionized form

↓

minimal diffusion into duodenal epith. cells, no gastric acid

↓

minimal mucosal damage

Dissolution test of 6 enteric-coated low-dose ASA tablets marketed in Indonesia

Sumirtapura YC, Setiawati A, Pamudji JS, Rachmawati H.

Med J Indones. 2009;18(3):161-6

Products tested

3 batches per product
6 tablets per batch

1) Cardio Aspirin® 100 mg
2) Aptor ® 100 mg
3) Ascardia ® 80 mg
4) Thrombo Aspilet ® 80 mg
5) Astika ® 100 mg
6) Farmasal ® 100 mg

Dissolution study

- Conducted at School of Pharmacy, ITB
  (Prof. Yeyet Cahyati – PI)
- Dissolution Tester acc. to USP/European Pharmacopoeia
- Basket 100 rpm
- 2 stages:
  - Acid stage : 0.1N HCl (pH = 1) 120 min.
  - Buffer stage : Phosphate buffer (pH = 6.8) 90 min.
- ASA dissolved was measured at:
  - end of acid stage (120 min.)
  - every 10 min. of buffer stage

Results of the Dissolution test

Acid resistance

ASA dissolved at end of acid stage (120 min)

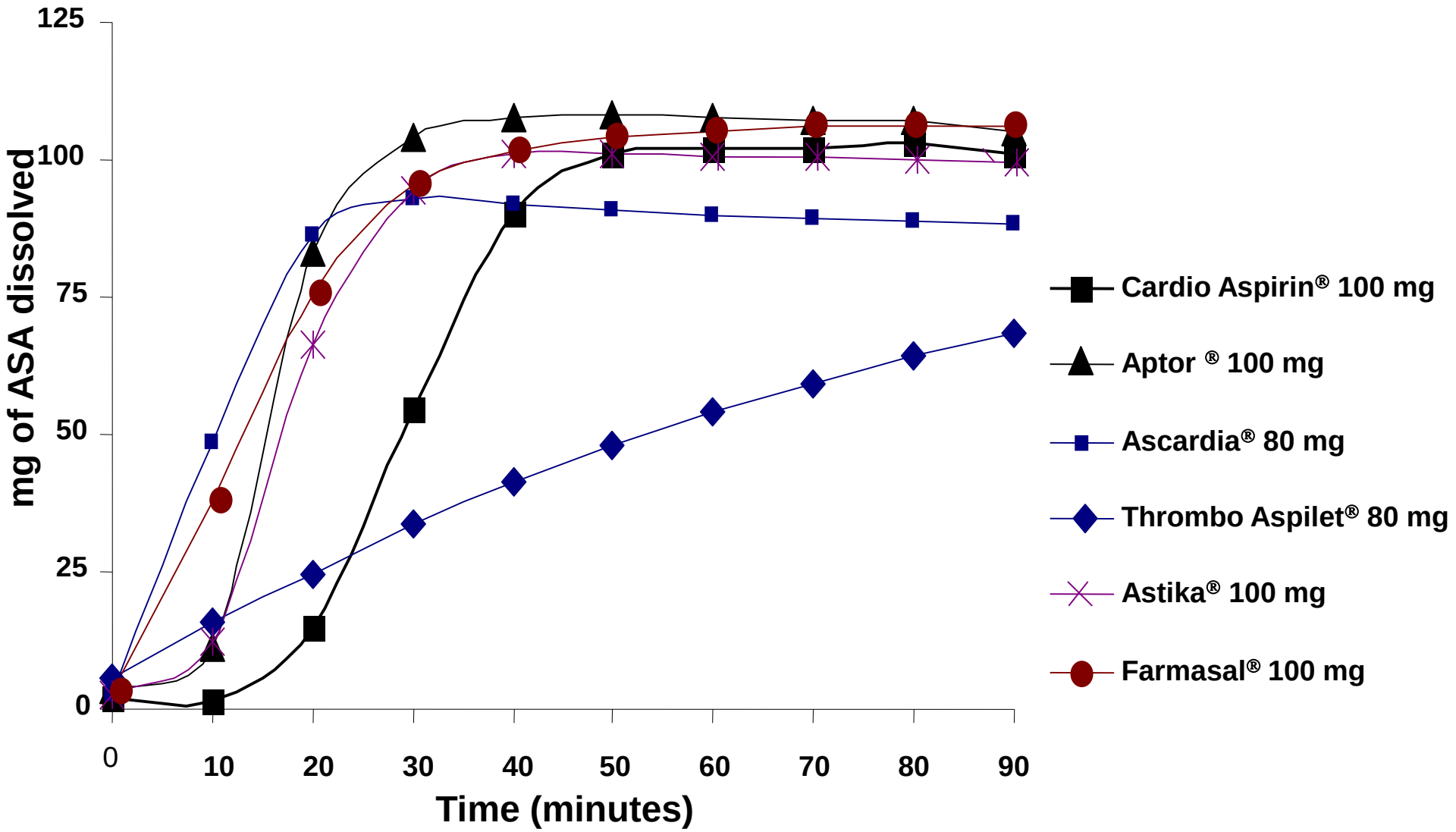
Cardio Aspirin® (100 mg)	1.79 mg (1.79%)
Aptor ® (100 mg)	3.70 mg (3.70%)
Ascardia ® (80 mg)	2.61 mg (3.26%)
Thrombo Aspilet ® (80 mg)	5.53 mg (6.92%)
Astika ® (100 mg)	2.74 mg (2.74%)
Farmasal ® (100 mg)	3.25 mg (3.25%)

Compendial requirement for enteric-coated tablets: < 10%

↓

All 6 products conformed to this requirement

Dissolution profiles in buffer stage



ASA dissolved at end of buffer stage (90 min)

Compendial requirement for
enteric-coated tablets: > 75%

↓

All products conformed to this requirement, except for one of the 3 batches of Thrombo Aspilet® (80 mg): 98.62%

55.11%

81.63%

ASA dissolved during buffer stage

- The variability between batches:
  - small for Cardio Aspirin® (0.56 - 8.89%)
    Aptor® (1.53 - 6.62%)
    Astika® (0.34 - 5.00%)
  - very high for Farmasal® (7.52-37.60) → inconsistency of the manufacturing process
- Thrombo Aspilet® also showed sustained-release properties

Salicylic acid released at end of buffer stage (end of dissolution test)

	% (range)
Cardio Aspirin® (100 mg)	3.47 (1.60 – 4.59)
Aptor ® (100 mg)	4.72 (4.18 – 5.62)
Ascardia ® (80 mg)	6.25 (5.20 – 7.69)
Thrombo Aspilet ® (80 mg)	11.90 (7.31 – 25.51)
Astika ® (100 mg)	10.90 (7.04 – 16.84)
Farmasal ® (100 mg)	5.73 (1.40 – 7.77)

Smallest for Cardio Aspirin®, followed by Aptor®
Highest for Thrombo Aspilet®, followed by Astika®

Deacetylation of ASA to salicylic acid

↓

ASA loses its activity to acetylate serine 529 at COX-1 enzyme in platelets

↓

ASA inactivation to produce persistent antiplatelet effect

Enteric-coated ASA :

ASA dissolves in the small intestine (pH = 6-7)

↓

ASA dissolves completely & > 99% in ionized form

↓

not all are absorbed

↓

lower bioavailability

↓

100 mg enteric-coated ASA is equivalent to 75 mg plain ASA (the smallest effective dose of ASA as an antiplatelet)

(Cox et al, 2006)

Enteric-coated ASA of 75 mg is estimated to deliver a dose equivalent to 50 mg plain ASA

(Cox et al, 2006)

may be true for enteric-coated 80 mg ASA in the present study : Ascardia®

Thrombo Aspilet®

Slow-release ASA 75 mg :

worse in terms of variation in platelet aggregation & serum TxB_2

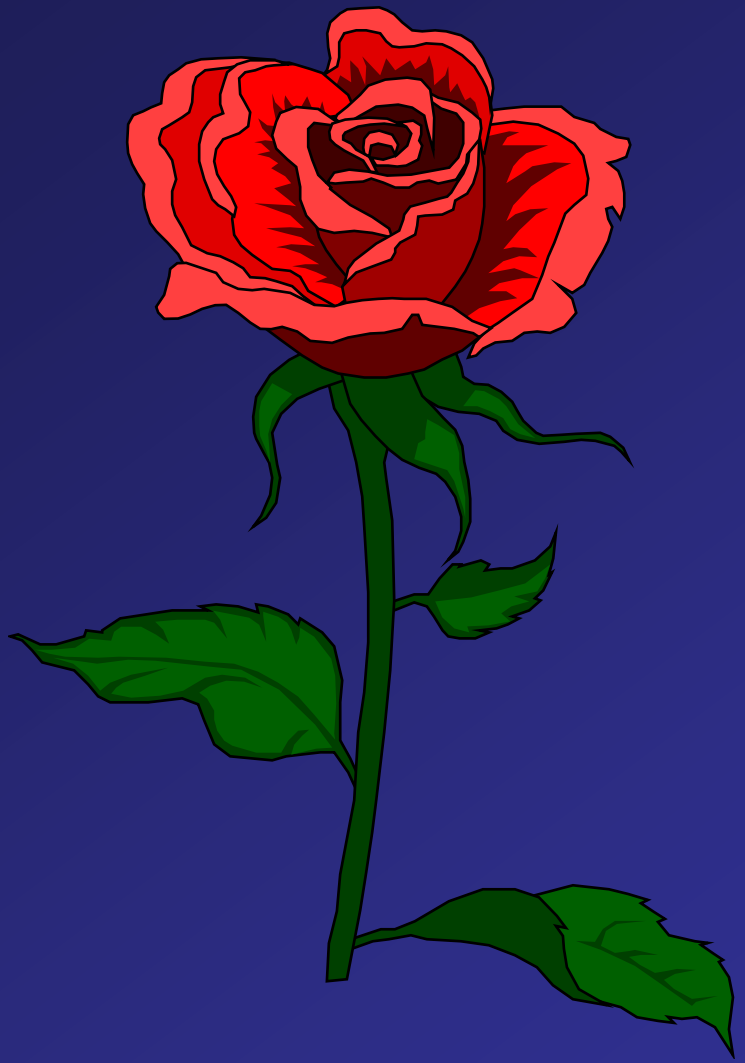
(Dooley et al, 2001)

may be true for Thrombo Aspilet®, which showed :

- **highest salicylic acid released at end of dissolution test**
- **high variability between batches in ASA dissolved at end of buffer stage, causing one of the batches fell below the compendial requirement for enteric-coated tablets**

Conclusions

- All of the 6 low-dose ASA tablets marketed in Indonesia are enteric-coated products
- Thrombo Aspilet® is also a sustained-release product
- Cardio Aspirin®, as the innovator product:
  - has the right dose for low-dose enteric-coated preparation (100 mg)
  - produces consistent ASA release between batches
  - the most stable towards deacetylation (antiplatelet inactivation)
  - developed by Bayer in 1993, and marketed in Indonesia 2004
- Aptor® was the only copy product that closely followed the above properties



Thank you