A Review of Naproxen/Aspirin Pharmacodynamic Interaction: The Kontakt Study Results

Presentation to the
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Drug Safety and Risk Management Advisory Committee

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Bayer OTC Analgesic Leadership

- Bayer is the manufacturer of Bayer Aspirin
  - Minor aches and pains
  - Acute MI and reduction of recurrent cardiovascular events (Professional labeling)

- Bayer also manufactures and markets OTC naproxen products under the brand name “Aleve”

- Naproxen is a fast acting and long lasting analgesic; making it an important option for many people seeking short term pain relief

- For decades naproxen products have been used safely and effectively
  - Over 1.5 billion cumulative world-wide consumer exposures
  - OTC doses up to 660 mg daily for up to 10 days

- No safety signal regarding CV thrombotic and overall CV events, with or without concomitant aspirin use, have been observed with OTC naproxen in postmarketing data

Kontakt Study Background

- Catella-Lawson (2001) demonstrated that ibuprofen interferes with serum thromboxane inhibition as measured by *ex vivo* serum TxB_2 during low dose aspirin administration

- FDA issued Science Letter and required ibuprofen label change (2006):
  - **Ask a doctor or pharmacist before use if you are** taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin

- Bayer submitted (2007) naproxen platelet inhibition studies to FDA – BAY 12110 (Schiff 2009) and BAY 12611 (Oldenhof 2010)
  - Data did not rule out possibility of an interaction

- Subsequent communication with FDA between 2010-2014 led to the design of the Kontakt study
  - The definition of the TxB_2 threshold was debated
  - Interaction study with immediate release (IR) aspirin and lowest OTC dose and dosing regimen of naproxen

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Disclosures

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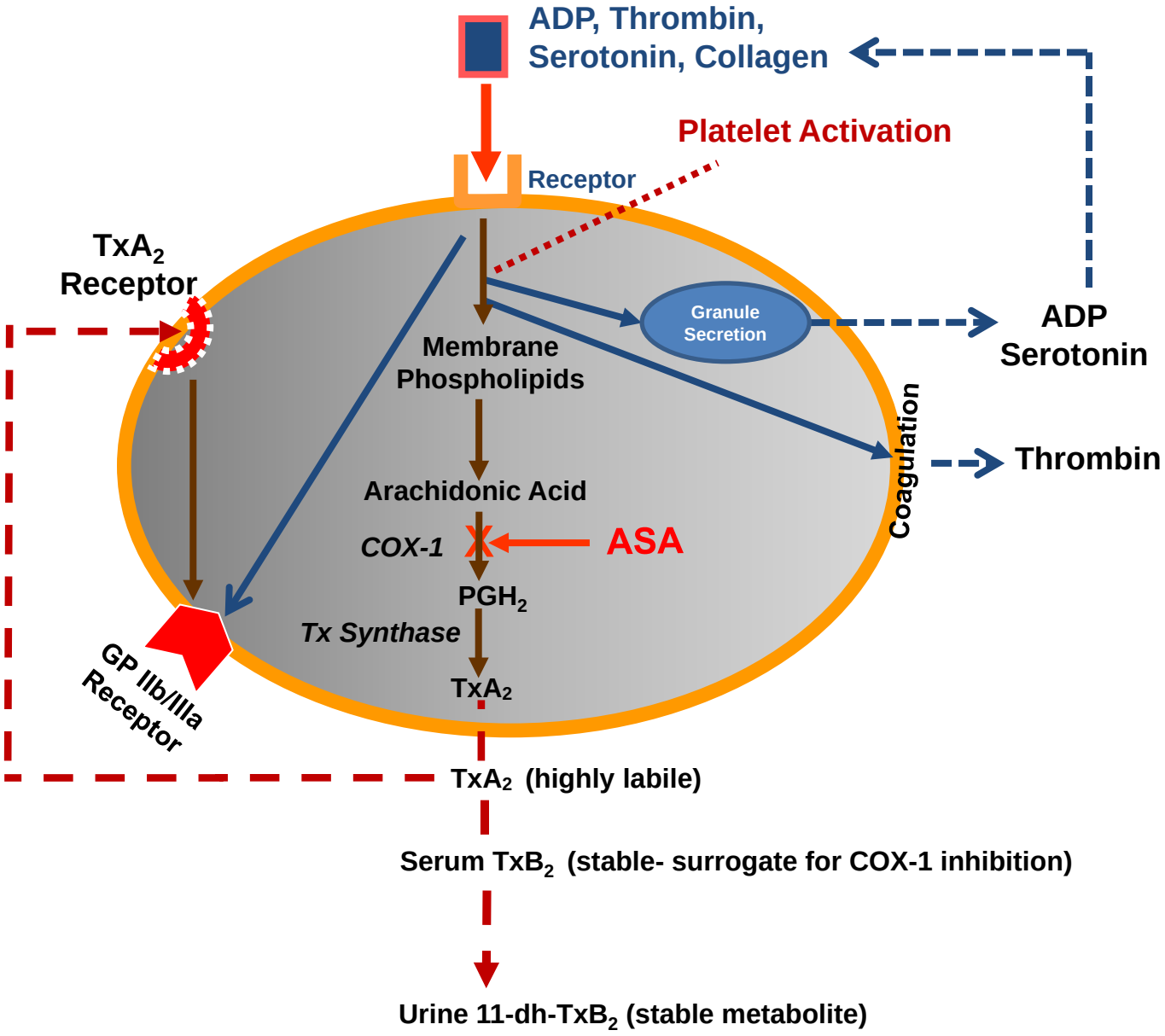
Janssen

Medicure

Merck

World Medical

Platelet Activation/ASA Pharmacology

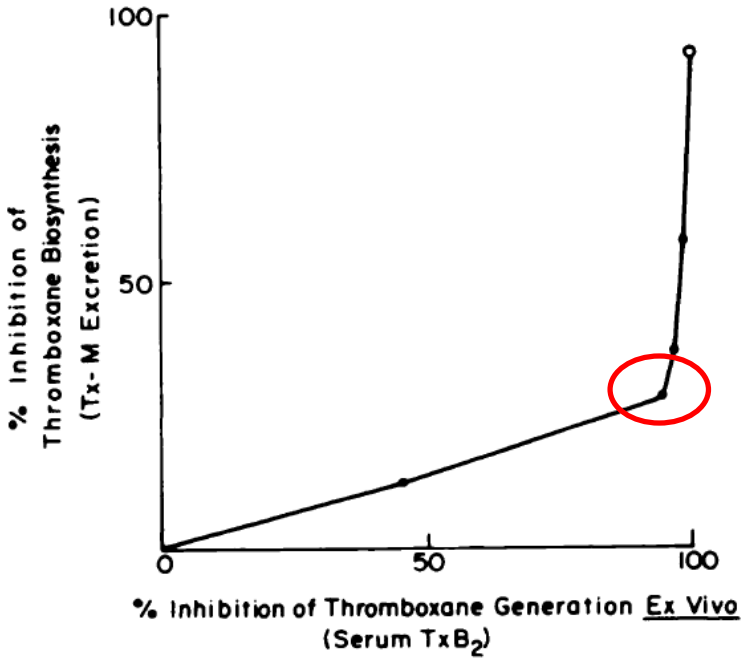


Adapted from Gurbel PA et al. *J Am Coll Cardiol*. 2007;50:1822-34

Controversy About What Degree of TxB_2 Inhibition Constitutes "Adequate" Platelet Inhibition

Is *ex vivo* TxB_2 inhibition ≥95% of baseline an appropriate surrogate threshold for "adequate" antiplatelet activity for *in vivo* TxA_2 inhibition?

(n = 12 healthy volunteers)

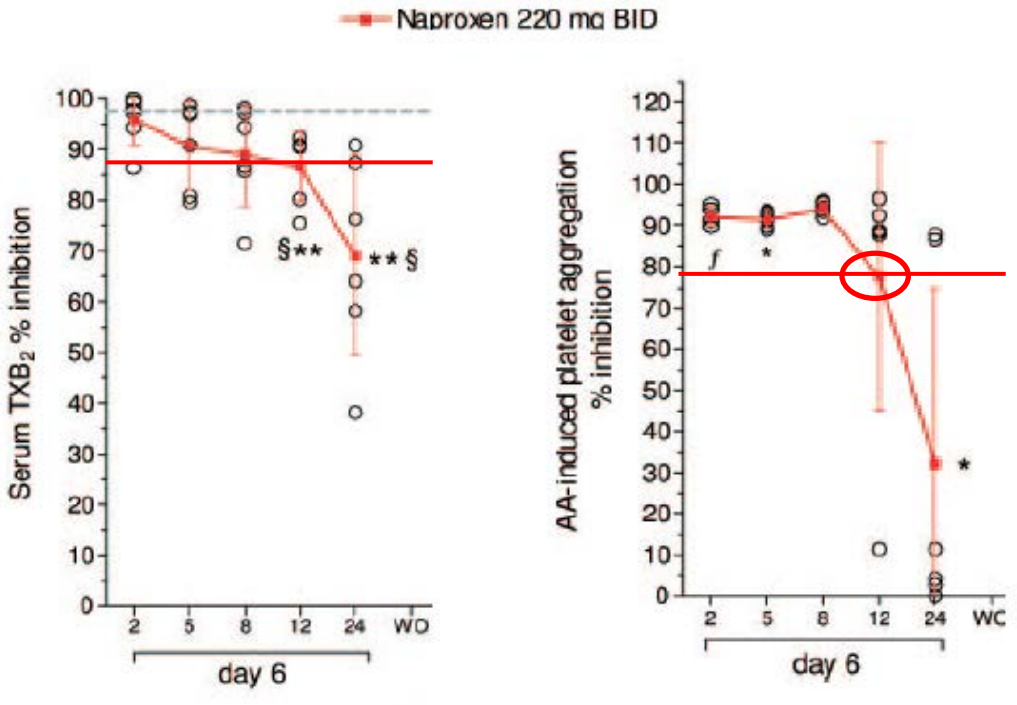


"*In vivo*" Tx biosynthesis (Tx-M excretion) is maintained to a substantial degree, unless >95% inhibition of thromboxane generation *ex vivo* is achieved

Reilly IA et al *Blood.* 1987;69:180-6

The key is what degree of TxB_2 inhibition is associated with inhibition of platelet aggregation

(n = 6 healthy volunteers)

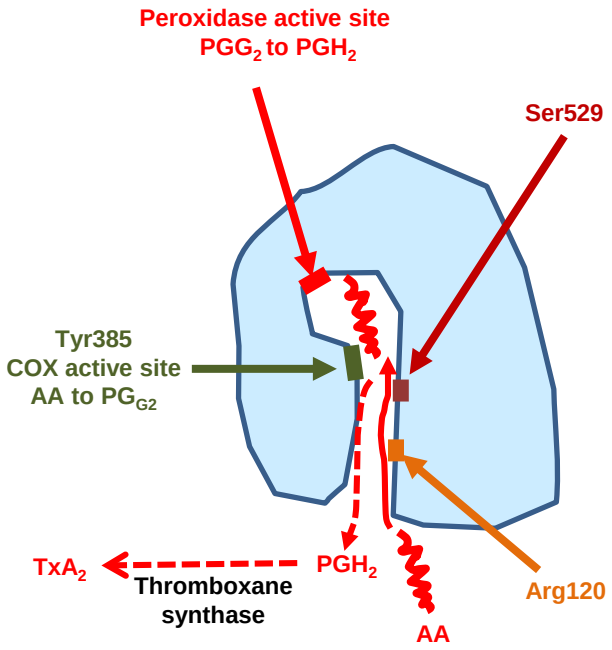


~87% mean TxB_2 inhibition is associated with ~75% inhibition of AA-induced aggregation

Capone ML et al. *J Pharmacol Exp Ther*. 2007;322:453-60

ASA and Naproxen Interaction

Cyclooxygenase -1 Enzyme

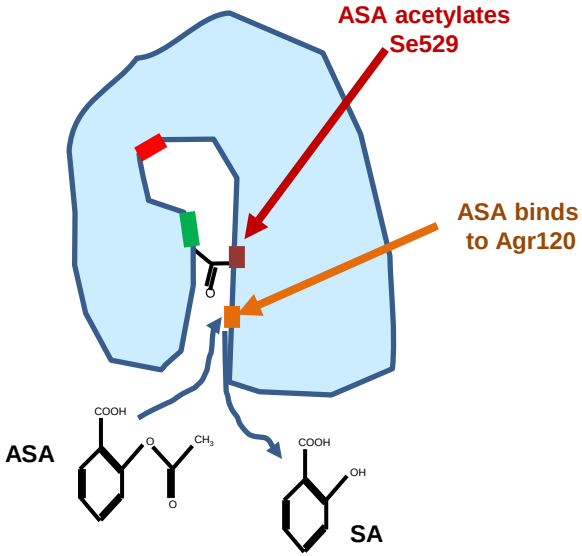


1) AA converted into PGG_2 at Tyr385

2) PGG_2 is converted to PGH_2 at peroxidase active site

3) PGH_2 converted to TxA_2 by tissue specific thromboxane synthase

Antiplatelet Effect of ASA

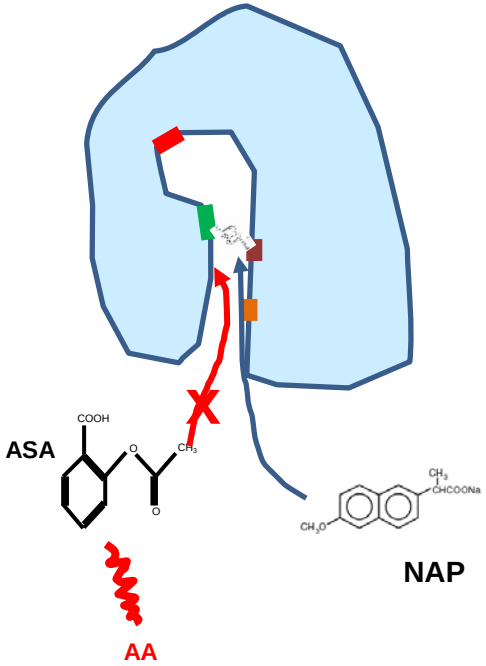


1) ASA binds to Arg120

2) Irreversibly acetylates Ser529

3) Blocks AA access to peroxidase active site

ASA and NAP Interaction



1) NAP reversibly prevents binding of ASA and AA to COX-1

ASA and Naproxen Interaction

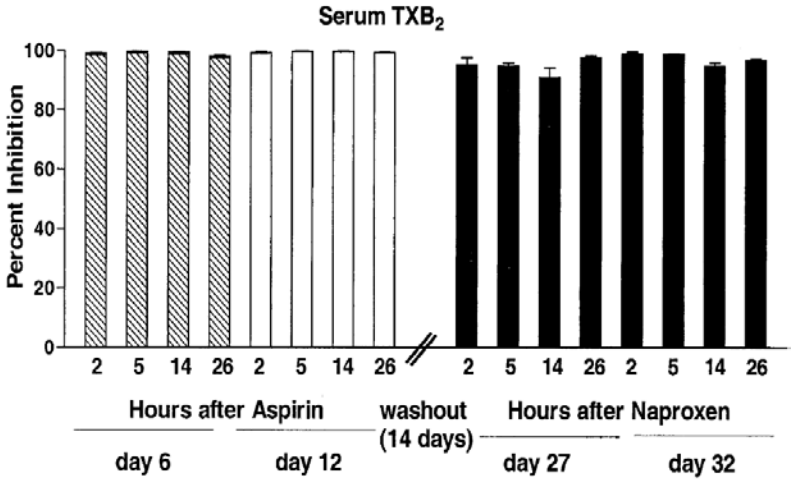
1. Capone ML et al. *J Am Coll Cardiol. 2005;45:1295–301*

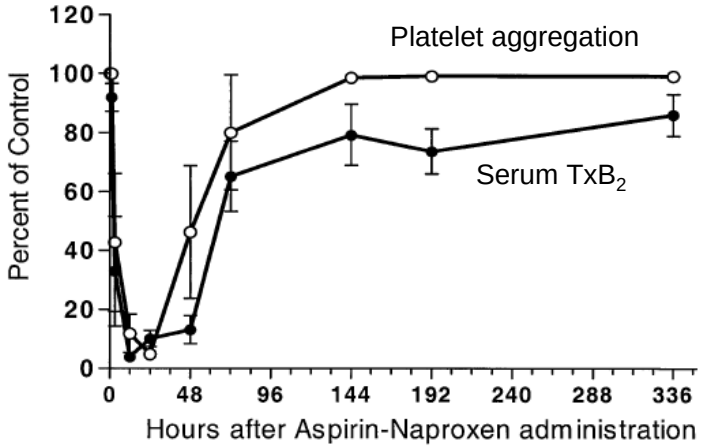
Study 1
(n= 4 healthy volunteers)

100 mg IR ASA for 6 days
- then, ASA 2 h before 500 mg NAP BID for 6 days
- then, 14 day washout
- then, 500 mg NAP BID 2 h before ASA for 6 days

Study 2
(n= 5 healthy volunteers)

- single dose 100 mg IR ASA + 500 mg NAP





The inhibition of serum TxB_2, platelet aggregation and urinary 11-d-TxB_2 levels by ASA alone was not significantly altered by the co-administration of NAP, given either 2 h after ASA or in reverse order

The rapid recovery of platelet COX-1 activity and function supports the occurrence of a PD interaction between NAP and ASA

ASA and Naproxen Interaction

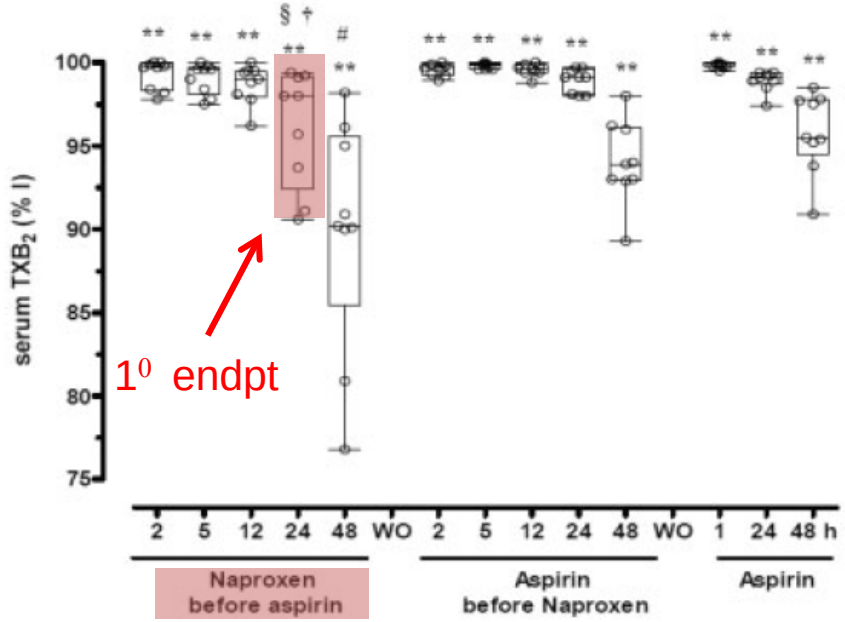
2. Anzellotti P et al. *Arthritis Rheum. 2011;63:850-9*

- 6 days of 3 different treatments separated by 14 day washout:

  1) 220 mg NAP BID 2 h before 100 mg IR ASA
  2) 100 mg IR ASA 2 h before 220 mg NAP BID
  3) 100 mg IR ASA alone

- Primary endpoint: TxB_2 inhibition 24 h post NAP given 2 h pre ASA on Day 6

(n=9 healthy volunteers)



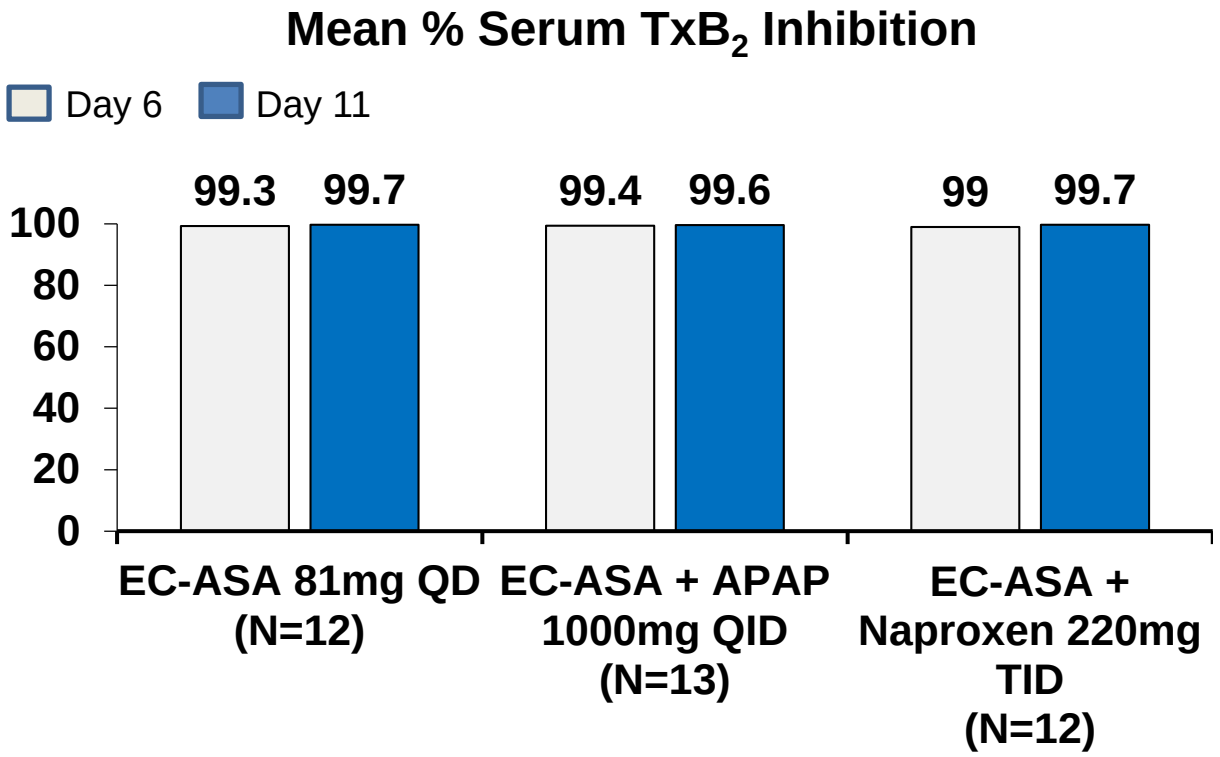
220 mg NAP BID given 2 h before 100 mg IR ASA interferes with inhibition serum TxB_2 afforded by ASA

The interaction was smaller when giving ASA 2 hours before NAP

ASA and Naproxen Interaction

3. Oldenhof J et al. *CMRO* 2010;26:1497-1504

- 5 days of 81 mg EC-ASA qd followed by:
  - 5 days of 81 mg EC-ASA QD
  - 5 days of 81 mg EC-ASA QD + 220 mg NAP TID
  - 5 days of 81 mg EC-ASA QD + 1 g acetaminophen QID
- Primary endpoint: TxB_2 inhibition on Day 11



The anti-platelet effect of EC-ASA 81 mg once daily was maintained following its co-administration with maximum OTC doses of NAP or acetaminophen

Objectives of the Kontakt Study

- Investigate whether concurrent administration of 220 mg once (QD) or twice (BID) daily immediate release (IR) naproxen sodium (NAP) tablet results in a PD interaction when combined with a once daily low-dose 81 mg IR aspirin (ASA) chewable tablet

- Investigate whether the interval between NAP and ASA dosing influence a potential PD interaction

Gurbel PA et al. *J Thromb Thrombolysis.* 2018;45:18-26.

Kontakt: Study Design

Randomized, controlled, open-label, parallel group study

6 day ASA alone run-in period (Days 1→ 6) → **10 day Concurrent treatment period (Days 7→16)** → **3 day ASA alone run-out period (Days 17→19)**

IR ASA dose = 81 mg QD

Naproxen sodium dose = 220 mg

Group 1: ASA + NAP QD at the same time

Group 2: ASA 30 min after NAP QD

Group 3: ASA 8 hours after NAP QD

Group 4: ASA only (control)

Group 5: ASA 30 min before NAP QD

Group 6: ASA 30 min after first dose of NAP BID (12 hours apart)

Gurbel PA et al. *J Thromb Thrombolysis.* 2018;45:18-26.

Methods and Analysis

Serum TxB_2:

- Baseline and Days 7, 16, 17, and 19 of the in-house treatment period at 1, 3, 6, 12, 18, and 24 h post-dose relative to the time of ASA
- TxB_2 ELISA Kit (Cayman Chemical Company, Ann Arbor, MI, USA; Cat# 501020)
- Platelet rich plasma TxB_2 measured as an exploratory analysis

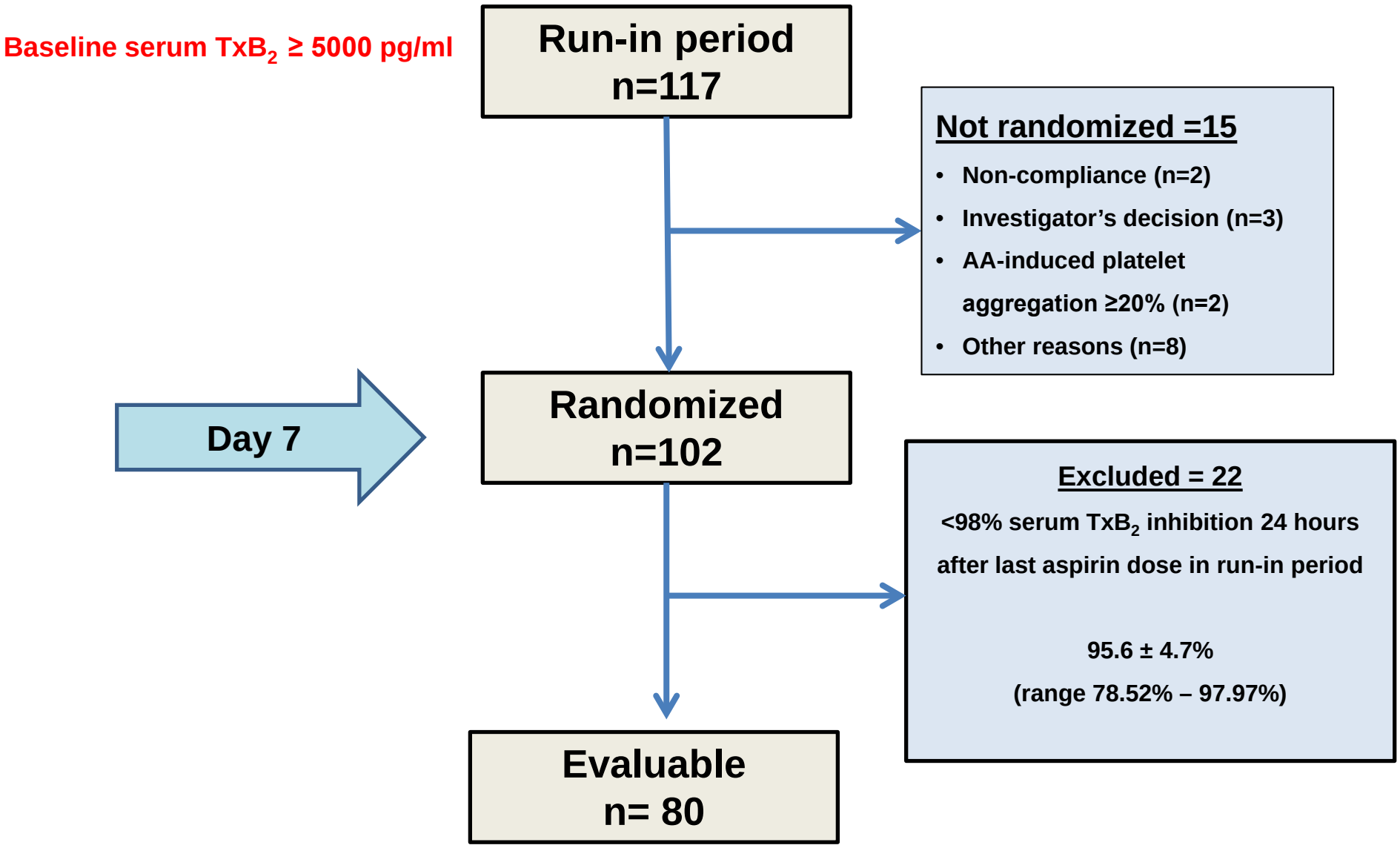
Primary PD analysis:

- Mean and lower bound of one-sided 95% CI for serum TxB_2 inhibition at 24 hours post-ASA administration after 10 days of concurrent treatment (Study Day 16 – "steady state")

PD interaction "defined" to occur when lower bound of 1-sided 95% CI for TxB_2 inhibition was <95%

Gurbel PA et al. *J Thromb Thrombolysis.* 2018;45:18-26.

Results: Subject Disposition

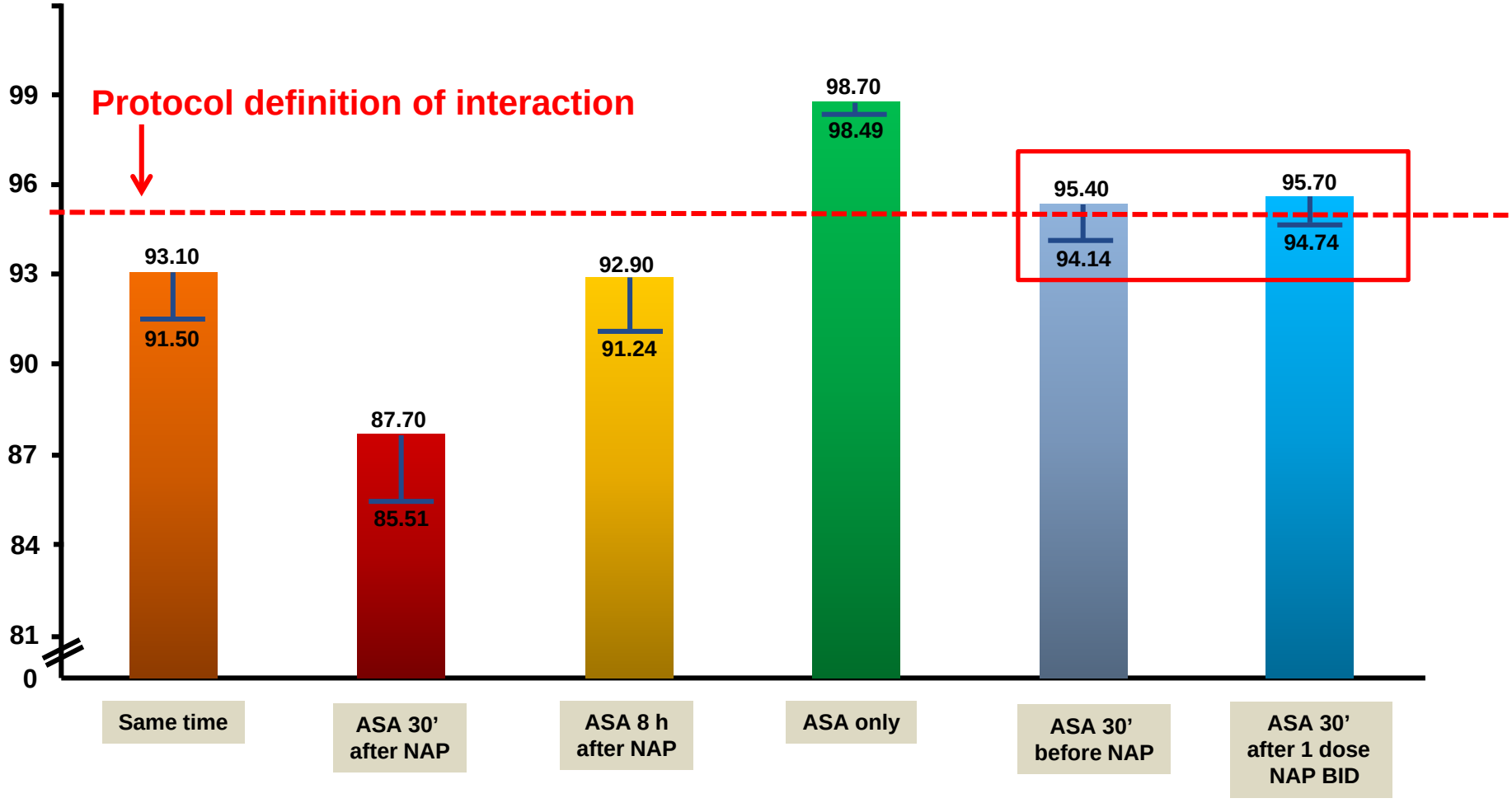


Gurbel PA et al. *J Thromb Thrombolysis.* 2018;45:18-26.

Results: Primary Outcome

Serum TxB_2 inhibition at 24 h post-aspirin administration after 10 Days of concurrent treatment

(mean + lower bound 1-sided 95% CI)

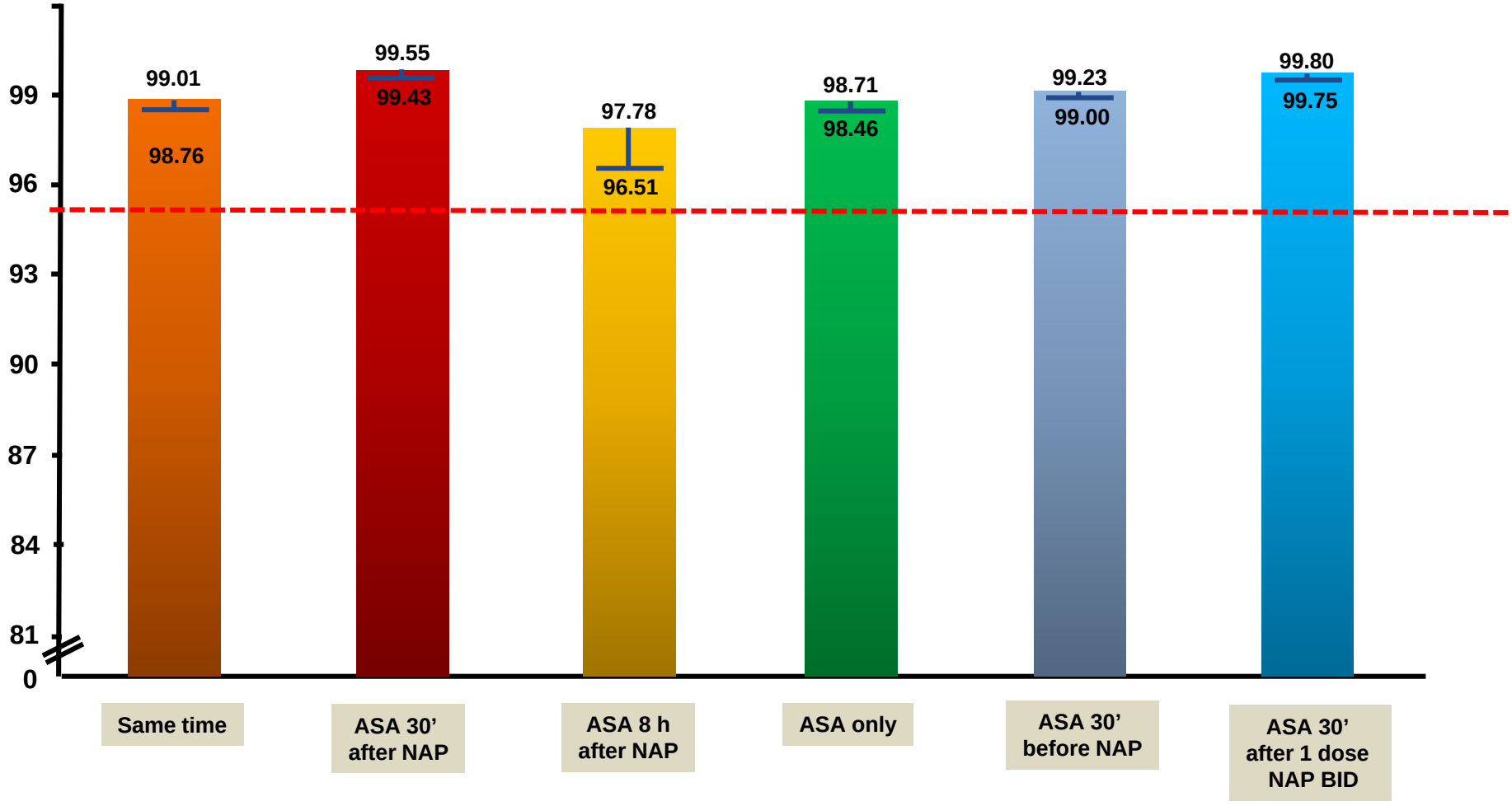


Gurbel PA et al. *J Thromb Thrombolysis.* 2018;45:18-26.

Results

Serum TxB_2 inhibition at 24 h post-aspirin administration after 1 Day of concurrent treatment (mean + lower bound 1-sided 95% CI)

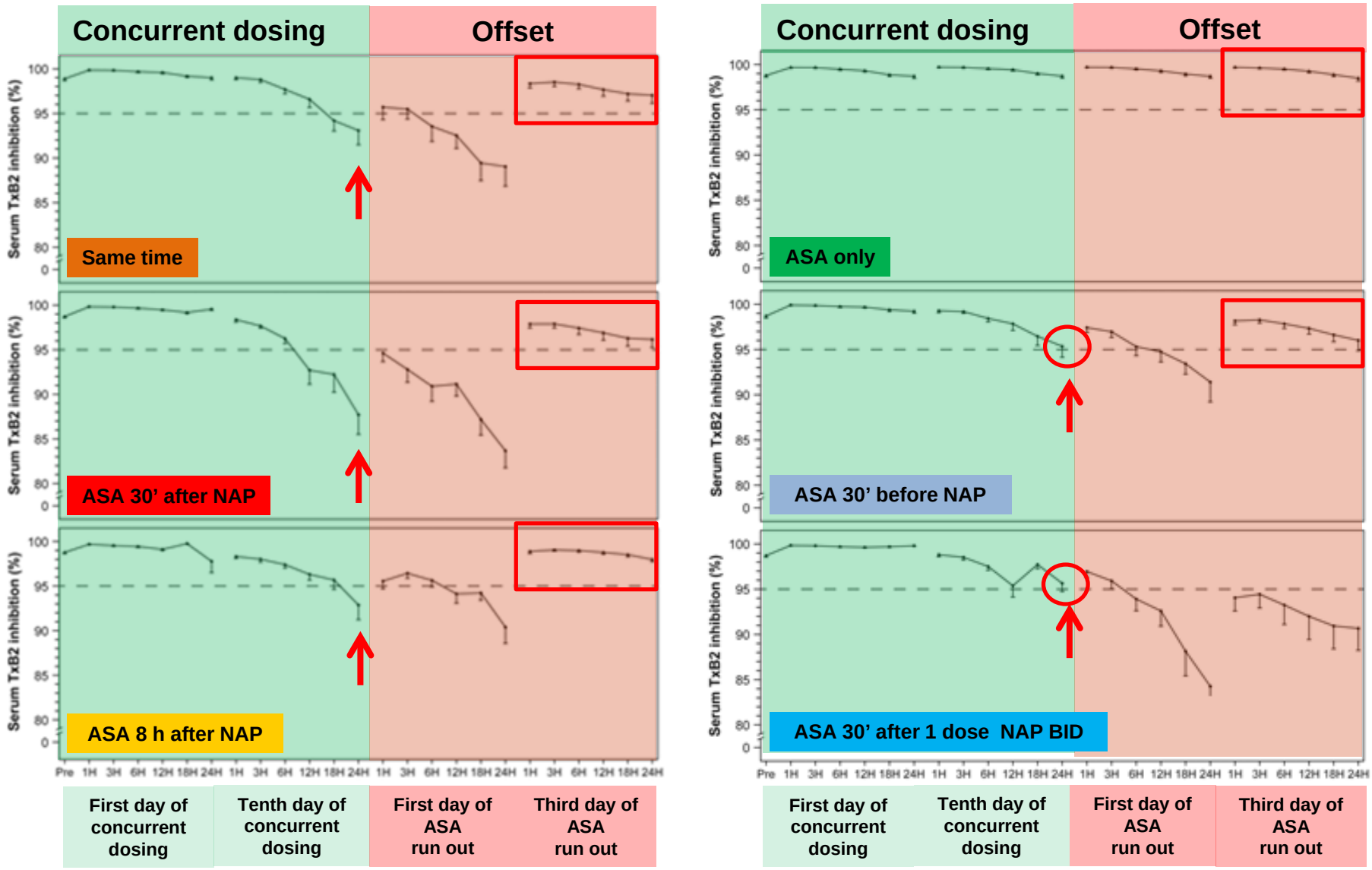
No loss of TxB_2 inhibition



Gurbel PA et al. *J Thromb Thrombolysis.* 2018;45:18-26.

Results

Serum TxB_2 inhibition – Individual time points



Gurbel PA et al. *J Thromb Thrombolysis.* 2018;45:18-26.

Conclusions

- After 10 days of concurrent treatment a pharmacodynamic interaction was observed in all of the concurrent treatment groups and persisted for at least one day after the end of the naproxen treatment period
- After the first day of concurrent treatment, all groups remained above the 95% TxB_2 inhibition threshold
- The degree of pharmacodynamic interaction was influenced by timing of aspirin and naproxen dosing
  - Least in group receiving aspirin 30 minutes before naproxen

Clinical Relevance

- The clinical relevance of this PD interaction remains uncertain
- No observational studies link the degree of serum thromboxane inhibition and CV outcomes
- No clinical outcome studies have been specifically designed and conducted to address potential aspirin interactions
- Meta-analyses and PRECISION study do not show increased CV risk with concurrent naproxen and aspirin

Bayer's Commitment to Responsible Labeling

- While uncertainty remains regarding the appropriateness of TxB_2 inhibition threshold and the clinical relevance of these findings, Bayer is committed to responsible labeling to guide appropriate physician and consumer use of its products
  - Updated its internal labeling templates for naproxen and aspirin and submitted label change applications around the world
    - Low dose aspirin and naproxen label changes have been initiated worldwide and updated labels are now effective in most countries
    - Recently PRAC (European Medicines Agency) reviewed the full body of data on naproxen-aspirin PD interaction, including the Kontakt and PRECISION data
      - Adopted Bayer's recommended labeling updates regarding the naproxen aspirin interaction
      - Concluded that the benefit-risk of naproxen sodium-containing products remains unchanged
- Nonetheless, Bayer proposed (2015) to harmonize the aspirin interaction labeling for all oral OTC non-aspirin NSAIDs:
  - "**Ask a doctor or pharmacist before use if you are** taking aspirin for heart attack or stroke, because naproxen may decrease this benefit of aspirin"