

Platelet Inhibition with PA32540 (a Tablet of Enteric-Coated Aspirin and Immediate-Release Omeprazole) + Clopidogrel Dosed Separately Is Greater Than Enteric-Coated Aspirin + Enteric-Coated Omeprazole + Clopidogrel Dosed Synchronously:

Results of A Randomized, Open-Label, Cross-Over Study

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Disclosures

Paul AGurbel:

Grants

Accumetrics, Daiichi Sankyo/Lilly, Haemonetics,
Multiplate, Nanosphere, Pozen, Sanofi Aventis

Speakers Bureau/ Honararia/ Consltant/Advisory Board

Astra Zeneca, Bayer, Daiichi Sankyo/Lilly, Merck, Medtronic, Novartis,
Pozen

Background

- Clopidogrel + ASA is the most widely used DAPT for ACS and PCI.
- Concomitant use of clopidogrel and a proton pump inhibitor (PPI), particularly omeprazole, was associated with attenuation of PD and clinical effects.¹
- Staggering delayed release (enteric coated) omeprazole with clopidogrel did not lessen PD interaction.²
- PA32540 :
 - tablet consisting of ASA (325 mg) + immediate release omeprazole (40 mg)
 - designed to minimize ASA-related GI toxicity while delivering a bioequivalent dose of ASA.
- Compared to 81 mg enteric coated aspirin, PA32540 associated with:
 - greater *in vivo* inhibition of thromboxane A₂ synthesis
 - similar upper gastrointestinal damage by Lanza score.³

1. Tantry US and Gurbel PA. *JACC Cardiovasc Interv.* 2011;4:365-80.

2. Ferreiro JL et al. *Circ Cardiovasc Interv.* 2010;5:436-41

3. Gurbel PA et al. *J Thromb Haemost.* 2009 (abstract)

Introduction

- Aspirin (ASA) is associated with an increased risk of upper gastrointestinal (UGI) damage.^{1,2}
- For cardioprotection, 50 million Americans take low-dose ASA, prompted, in part, by tolerability and safety concerns with higher doses.³
- Physicians tend to prescribe lower doses³
 - ASA 81 mg/d, 60%
 - ASA 325 mg/d, 35%
- However, the antiplatelet effects of low-dose ASA may not be equivalent to high-dose ASA.⁴

1) McQuaid KR and Laine L. *Am J Med.* 2006;119:624-38.

2) Yeomans ND et al. *Aliment Pharmacol Ther.* 2005;22:795-801.

3) Campbell CL et al. *JAMA.* 2007;297:2018-24.

4) Gurbel PA et al. *Circulation.* 2007;115:3156-64.

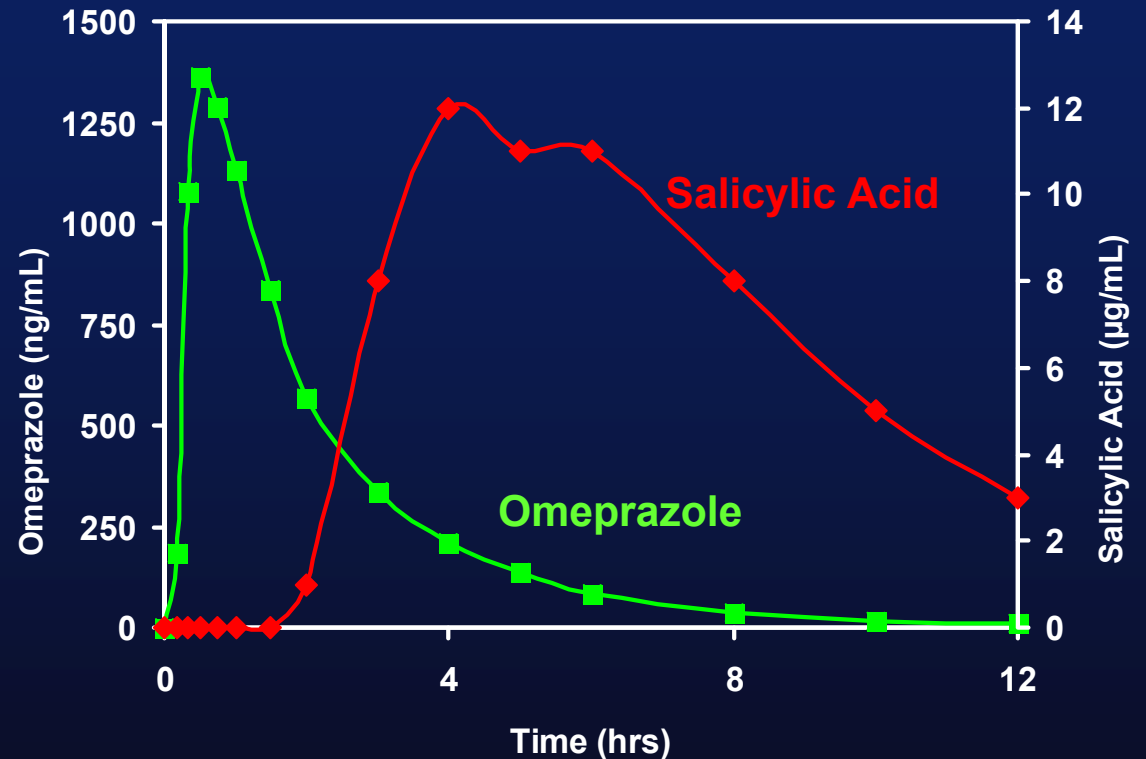
What is PA32540?

pH-sensitive film coat:
dissolves at pH >5.5



IR omeprazole (40 mg)
embedded in film coat

Coordinated and Sequential Release Profile¹

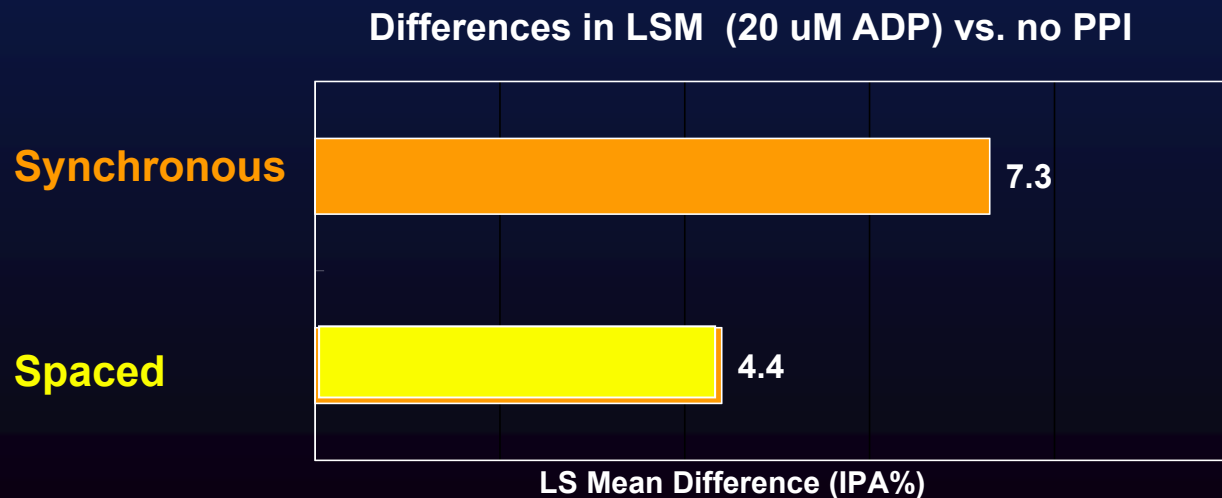


The tablet is unique in that omeprazole is not enteric-coated or buffered as it is in other PPI products. It is immediately released.
Omeprazole (40 mg) IR-T max = 32 min; DR-Tmax = 97 min²

1. Gurbel PA. et al. *J Thromb Haemost.* 2009 (abstract)
2. Wo JM. *Aliment Pharmacol Ther.* 2009;31:516-522.

Spacing Study

- Comparison of:
 - ECASA(325 mg) + C (300 mg/75 mg)
 - PA32540 + C (300 mg/75 mg) (synchronous)
 - PA32540 + C (300 mg/75 mg) (spaced 10 h)
- Interaction observed with synchronous PA32540+C vs. ECASA+C.
- Spacing PA32540 + C lessened interaction:



Objectives

Primary:

- IPA (20 μ M ADP, max.) after 7days, 2 h post-last dose:

Treatment A - (spaced 10h)

PA32540 + C (300mg/75mg)

VS.

Treatment B - (synchronous)

ECASA(81mg) + C (300mg/75mg)+

EC omeprazole (40mg, Prilosec)

Secondary:

- IPA (2mM AA) after 7days: **Treatment A vs. Treatment B**
- Safety

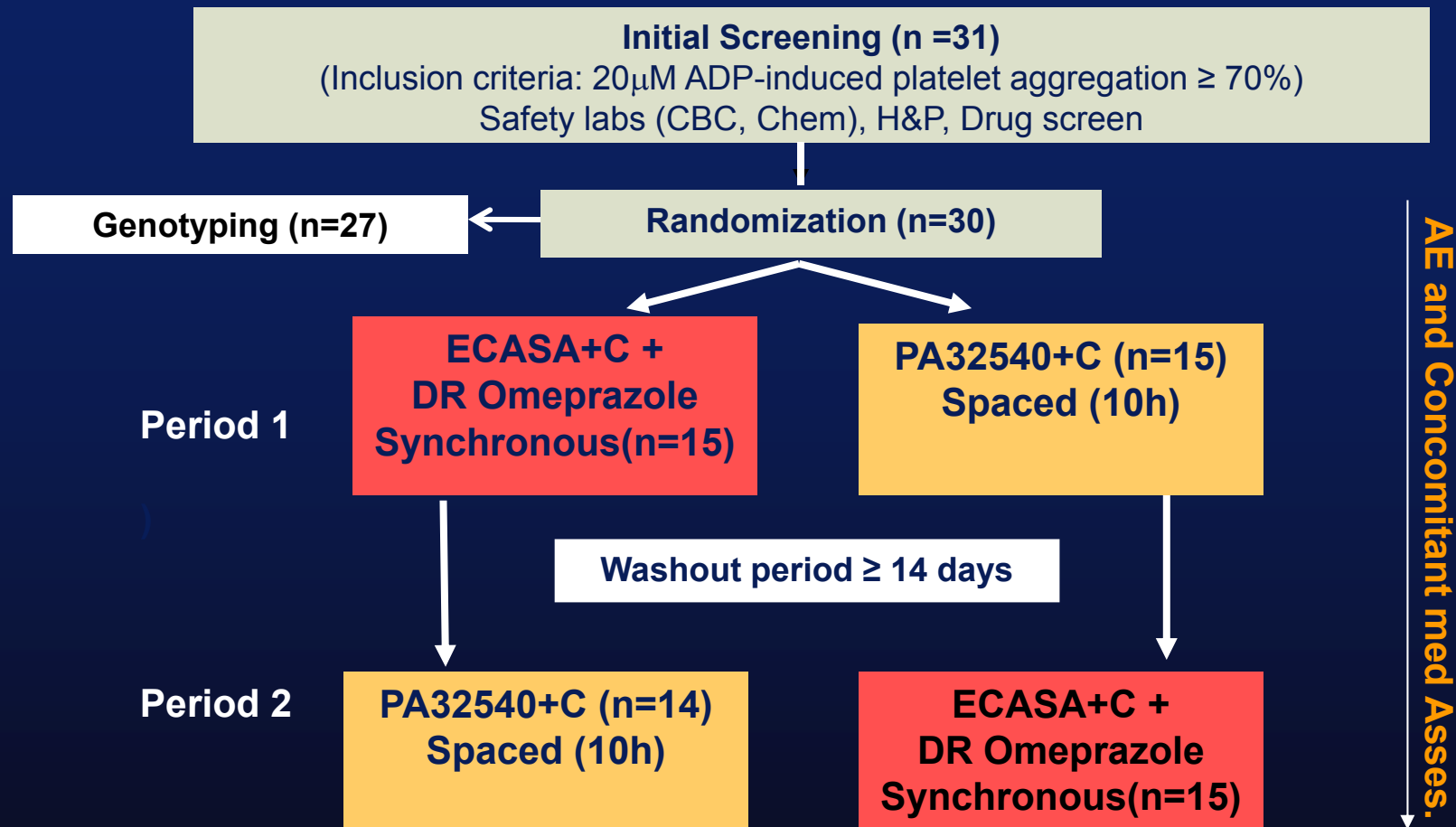
Study Criteria

Inclusion: Healthy subjects ≥ 40 years old

Exclusion:

- Acute, or chronic medical condition
- Allergy/intolerance to PPI, ASA, C
- GI disorder or surgery - impaired drug absorption
- $< 70\%$ screening platelet aggregation (20 μ M ADP, max.)
- PPI or P450 induc/inhib agent within 4 wks
- BMI outside range (19-32 kg/m²)
- Antiplatelet or NSAID within 2 wks
- Any tobacco product before (3 mo) and during the study
- Blood work outside normal limits

Study Design



- PFT at baseline and day 7 (2hrs after dosing) for each treatment period.
- No chocolate or caffeine products 48 hours prior to each blood draw.
- Administered with 240 mL water, standardized breakfast 1 hour after dosing
- Subjects on spaced therapy returned to Phase I unit in PM to receive clop (prior to dinner).

Statistics

Sample size calculation:

- 30 subjects per treatment (15 per seq in a crossover fashion)
- > 90% power, two-sample t-test at 5%, 10% mean IPA difference assuming mean IPA of 40% (spaced) and SD of treatment differences is 14%.

Statistics:

- Endpoint measure defined as $IPA (\%) = [1 - PA_7 / PA_0] \times 100\%$.
- Differences in least-squares (LS) means with 95% CI between treatments.

Results

Study Population

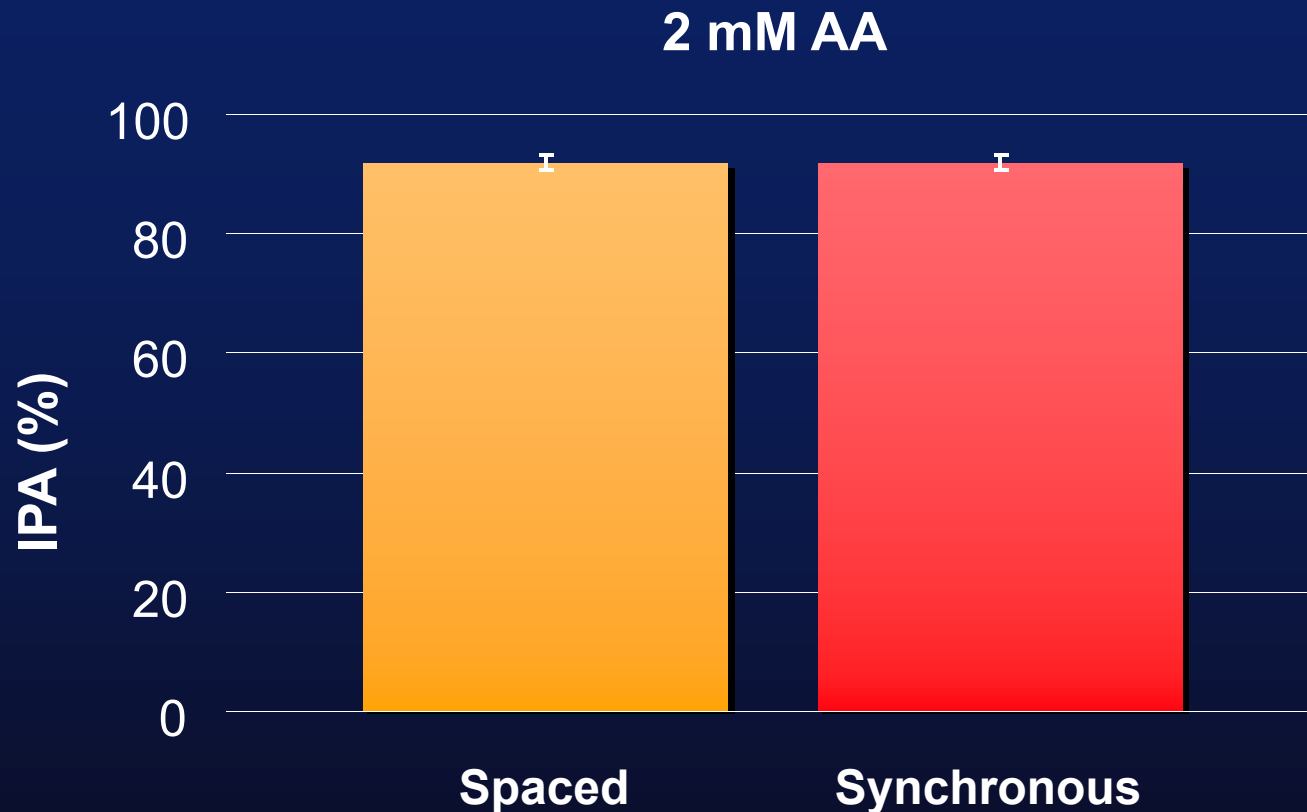
- 29 of 30 completed both treatments
- **Demographics:** mean age -49 yrs, mean BMI-27, 57% women, 77% Caucasian

Adverse Events

- No serious AE's
- Subjects with any AE's
 - Spaced (n=14, 48%); Synchronous (n=16, 53%)

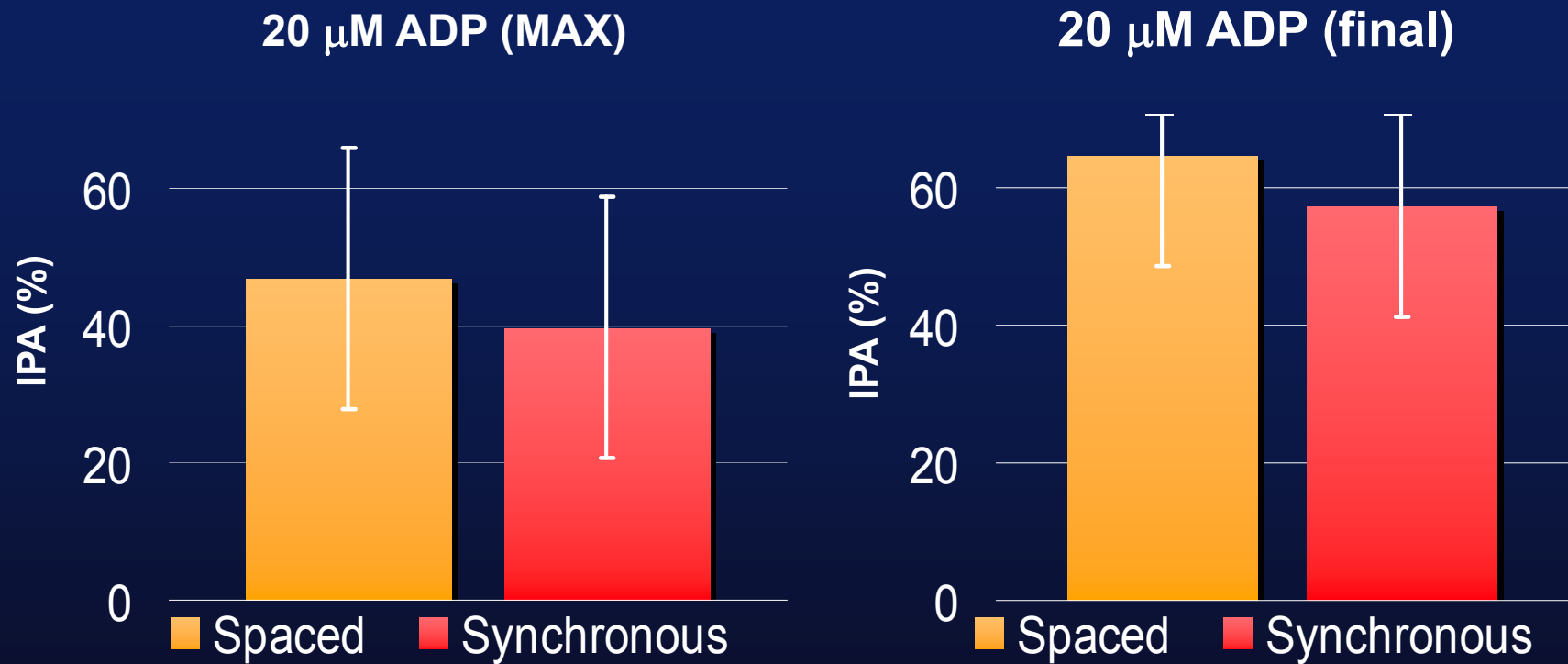
	Spaced	Synchronous
CNS (Headache, Dizziness)	7 (24%)	5 (17%)
Skin (Ecchymosis)	6 (21%)	4 (13%)
GI (flatulence, constipation)	3 (10%)	6 (20%)

Aspirin Response: Spaced and Synchronous



	LS Mean Diff. (95% CI)	p-value
IPA (2 mM AA)	0.1 (-3.3,3.4)	0.975

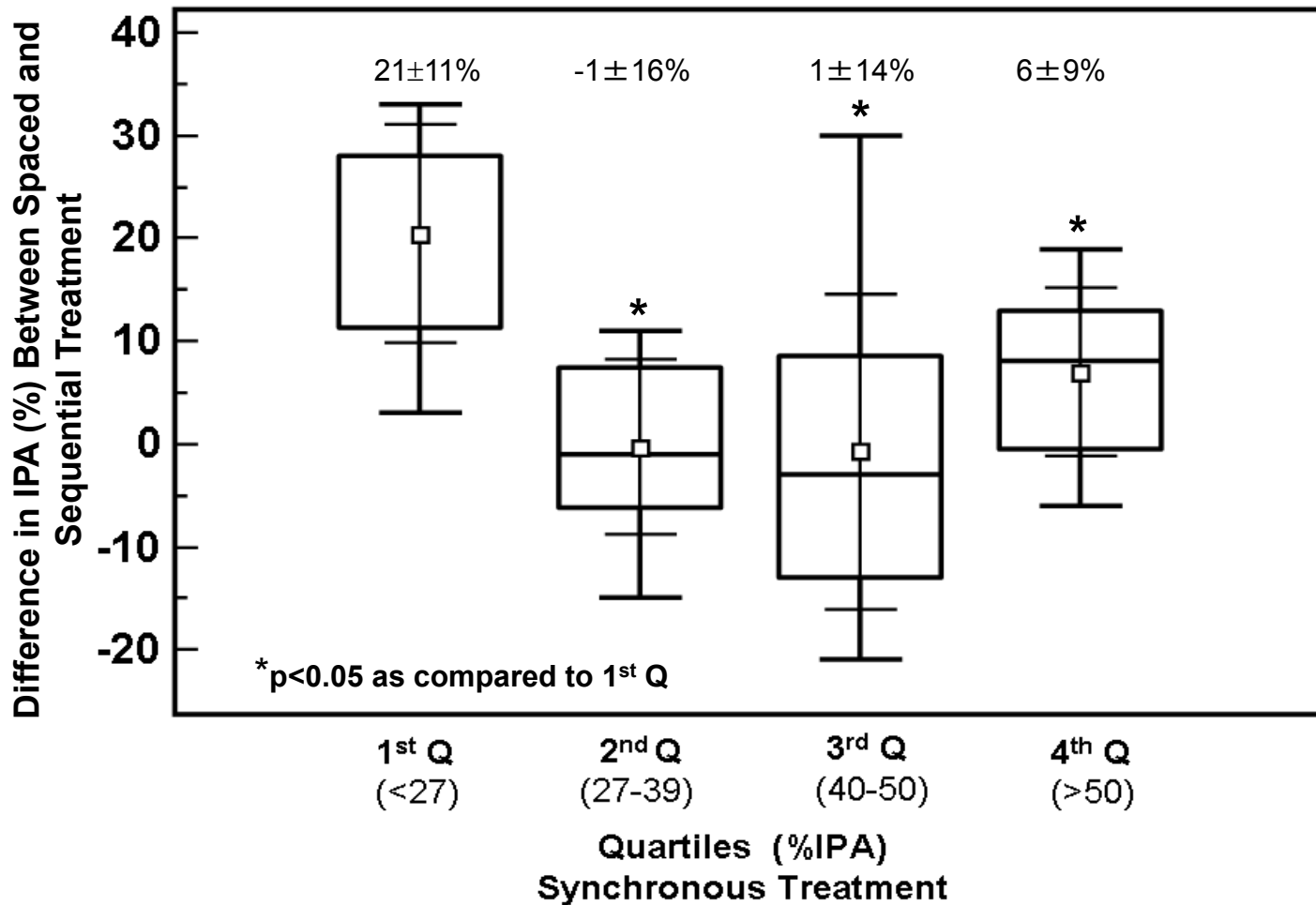
Clopidogrel Response: Spaced and Synchronous



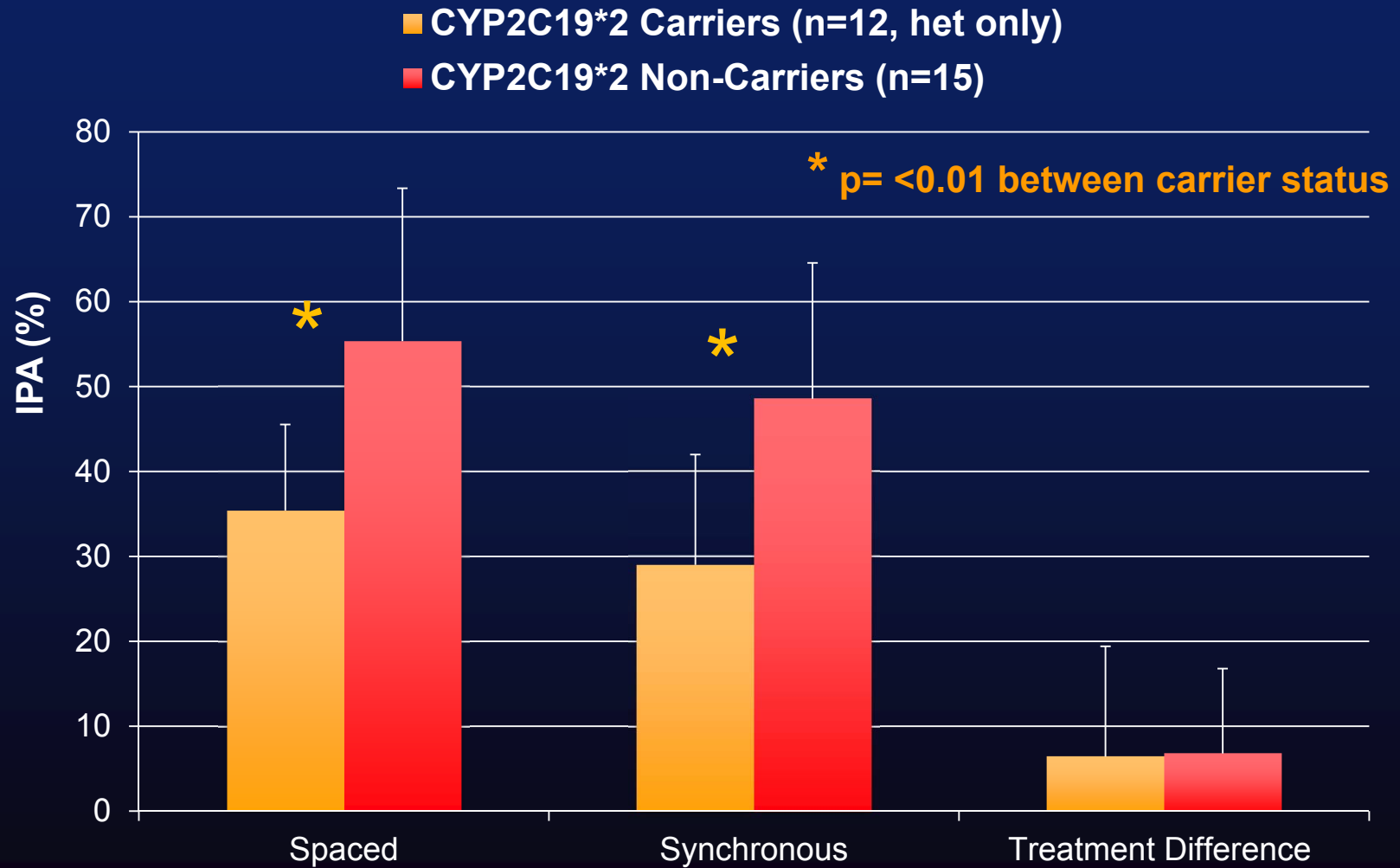
	LS Mean Diff. (95% CI)	p-value
IPA 20 μM ADP (max)	7.2 (2.5,11.9)	0.004
IPA 20 μM ADP (final)	8.2 (2.6, 13.8)	0.006

Effect of Spaced Treatment:

Relation to IPA During Synchronous Administration



Influence of CYP2C19*2 Carriage on Effect of Spacing



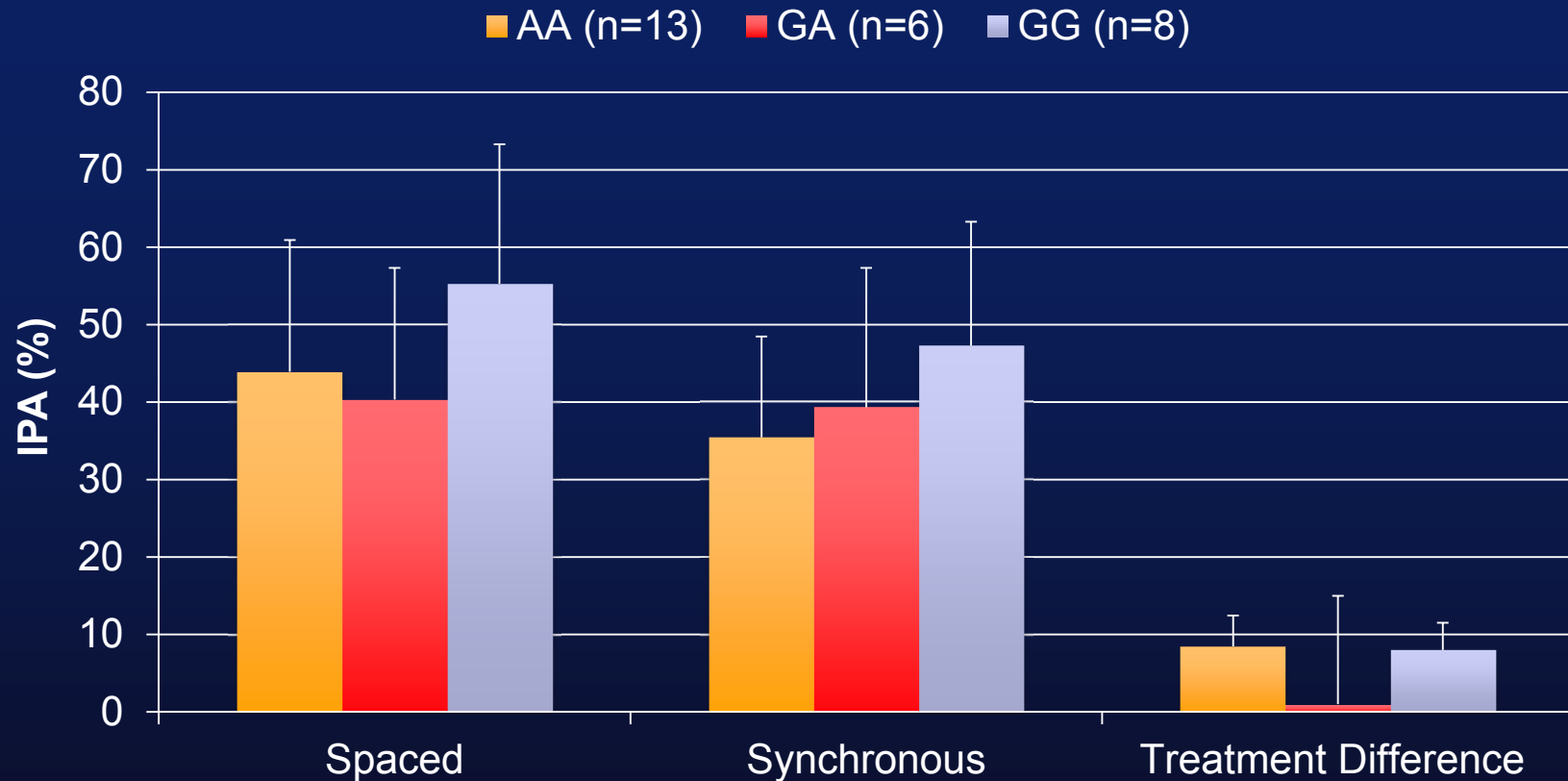
Limitations

- **No measurement of pharmacokinetics**
- **No comparison with spaced DR omeprazole**
- **No evaluation of other effects of ASA (collagen-induced aggregation, etc)**
- **No evaluation of high dose omeprazole or other doses of ASA**
- **Evaluation not in stent/CV population**

Conclusions

- **PA32540, a novel combination of aspirin and immediate release omeprazole, when dosed 10 hours apart from clopidogrel, was associated with greater IPA than synchronous administration of ECASA + clopidogrel+ DR omeprazole.**
- **Patients with the poorest IPA during synchronous administration appear to benefit the most by spacing.**
- **The beneficial effect of spacing on IPA does not appear to be influenced by *2 carrier state.**
- **The effects of PA32540 and ECASA (81mg) on the inhibition of cyclo-oxygenase, as measured by arachidonic-acid-induced aggregation, were the same.**
- **These findings are directly relevant to the treatment of patients with high gastrointestinal risk who require DAPT and gastroprotection.**

ABCB1 (C3435T variant)



- CVD studies on ABCB1 C3435T variant have shown to effect clopidogrel absorption as measured by PK variables (intestinal absorption and metabolic activation).¹
- However, PD studies using ADP-induced PA have found no significant association.²

1. Simon et al. *N Eng J Med* 2009;360:363-375

2. Shuldiner et al. *JAMA* 2009;302 (8):849-857