

Prasugrel For Reduction of Cardiovascular Events in Patients with Acute Coronary Syndrome (ACS)

**Cardiovascular and Renal Drugs Advisory Committee
Silver Spring, Maryland
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Prasugrel: Points for Discussion

- **Efficacy**
 - Time course
 - Subgroups with marginal effectiveness
- **Safety**
 - Deaths
 - Bleeding
 - Subgroups at particular risk
 - Neoplasia
- **Quality**
 - Form conversion from salt to base

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Prasugrel: Evidence of Effectiveness (1)

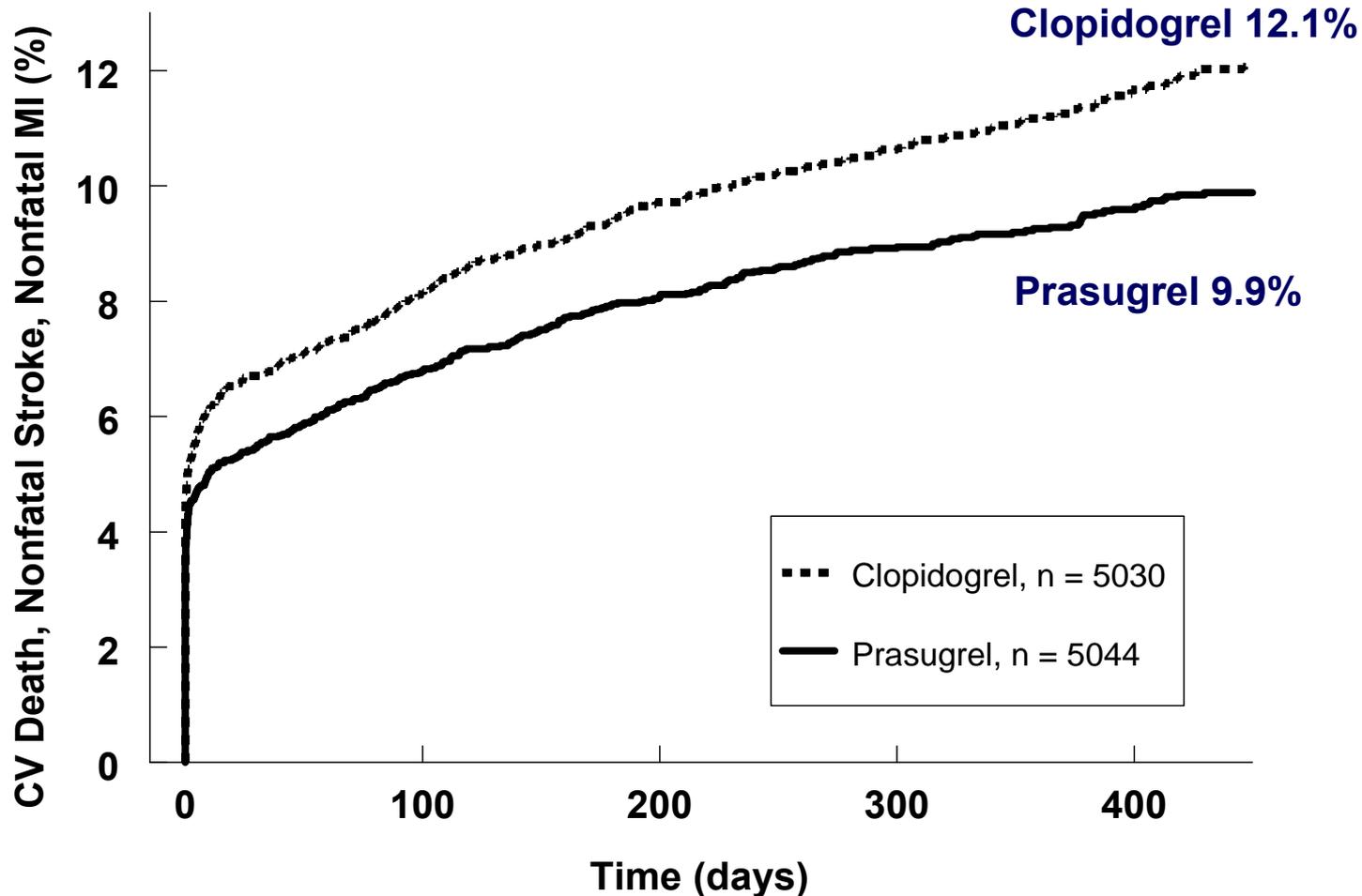
TRITON-TIMI 38 (“Study TAAL”)

- Phase 3, multinational, randomized, double-blind, double-dummy, active-controlled study
- Subjects with acute coronary syndrome (ACS), scheduled to undergo percutaneous coronary intervention (PCI)
- Randomized 1:1 to oral prasugrel (60-mg load; 10-mg daily maintenance) or clopidogrel (300-mg load; 75 mg daily maintenance)
- Hypothesis: prasugrel plus aspirin is superior to clopidogrel plus aspirin

Prasugrel: Evidence of Effectiveness (2)

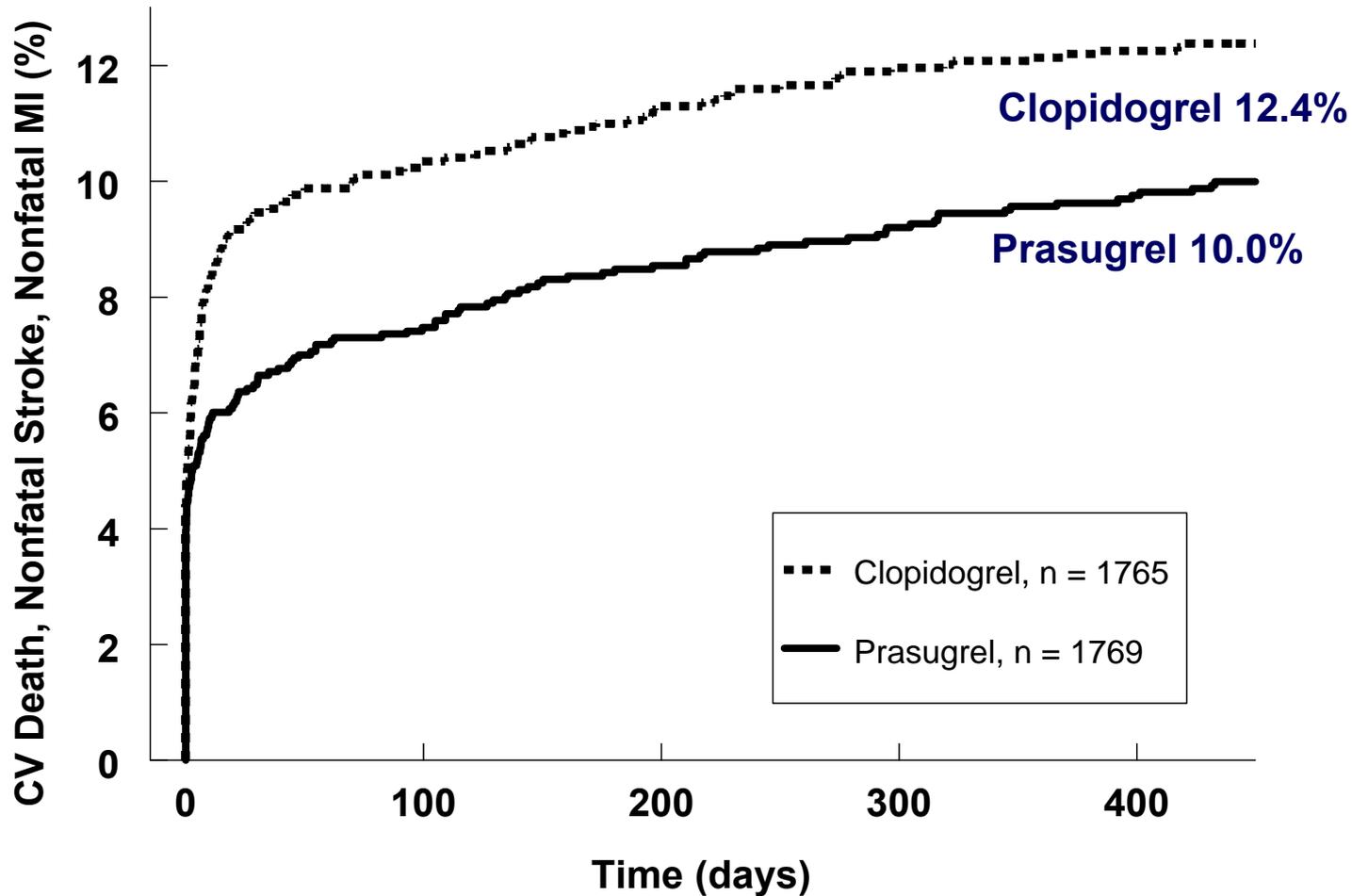
- Randomization stratified by presentation:
 - Unstable angina or non-ST-segment elevation myocardial infarction (UA/NSTEMI)
 - versus
 - ST-segment elevation myocardial infarction (STEMI)
- Composite endpoint (“triple endpoint”):
 - cardiovascular death
 - nonfatal myocardial infarction
 - nonfatal stroke
- 717 principal investigators, 725 study centers
- 13,608 subjects enrolled
- Median follow-up = 15 months (mean = 12 months)

Primary Efficacy Endpoint: Non-STEMI /UA



HR=0.82, 95% CI, 0.73-0.93; p=0.002

Primary Efficacy Endpoint: STEMI



HR=0.79, 95% CI, 0.65-0.97; p=0.019

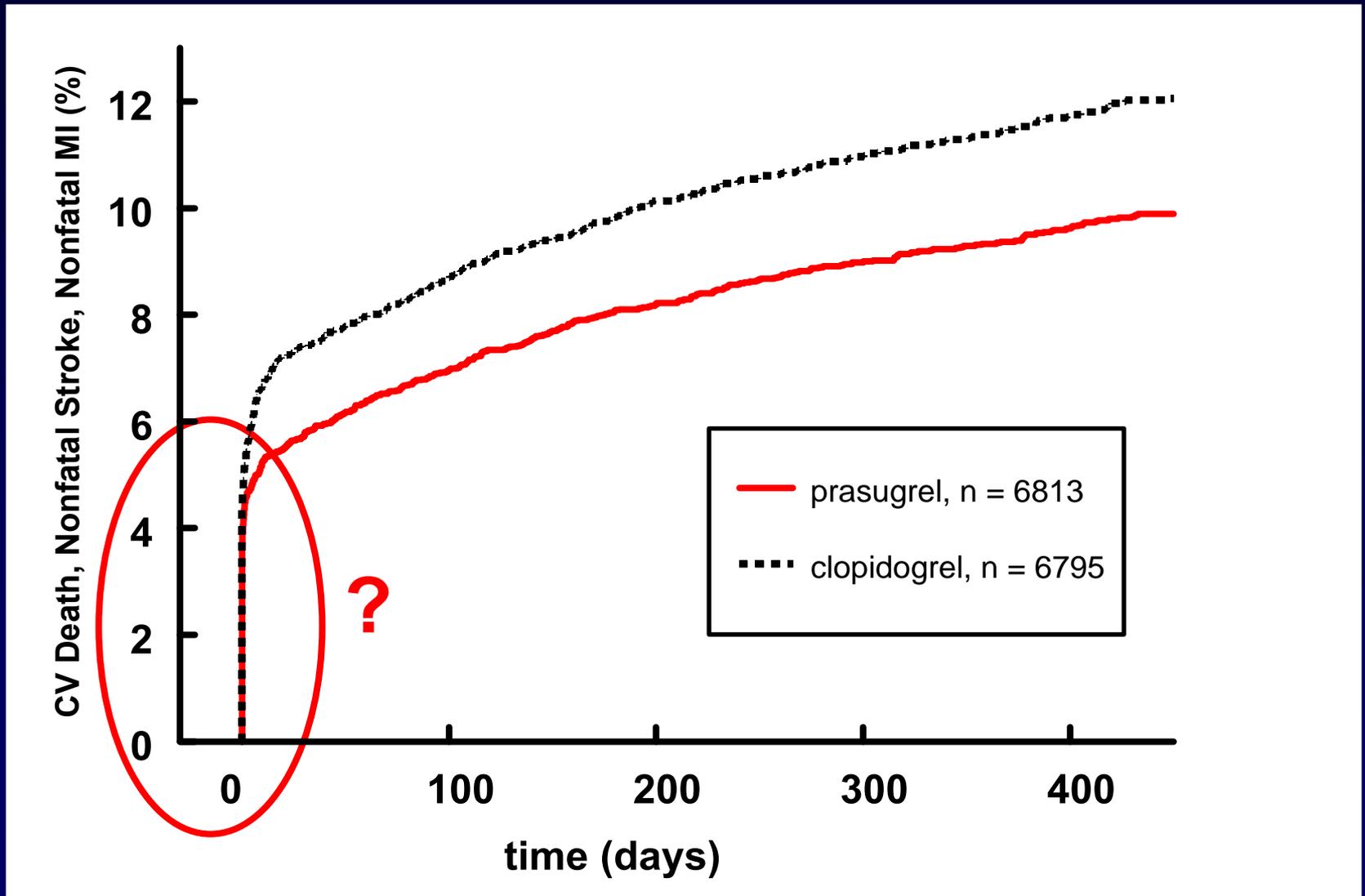
Components of Primary Efficacy Endpoint:

Patient population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
	N	n	%	N	n	%		
<u>CV Death</u>								
UA/NSTEMI	5044	90	1.8	5030	92	1.8	0.98 (0.73, 1.31)	0.89
STEMI	1769	43	2.4	1765	58	3.3	0.74 (0.50, 1.09)	0.13
All ACS	6813	133	2.0	6795	150	2.2	0.89 (0.70, 1.12)	0.31
<u>Nonfatal MI</u>								
UA/NSTEMI	5044	357	7.1	5030	464	9.2	0.76 (0.66, 0.87)	<0.001
STEMI	1769	118	6.7	1765	156	8.8	0.75 (0.59, 0.95)	0.02
All ACS	6813	475	7.0	6795	620	9.1	0.76 (0.67, 0.85)	<0.001
<u>Nonfatal Stroke</u>								
UA/NSTEMI	5044	40	0.8	5030	41	0.8	0.98 (0.63, 1.51)	0.92
STEMI	1769	21	1.2	1765	19	1.1	1.10 (0.59, 2.04)	0.77
All ACS	6813	61	0.9	6795	60	0.9	1.02 (0.71, 1.45)	0.93

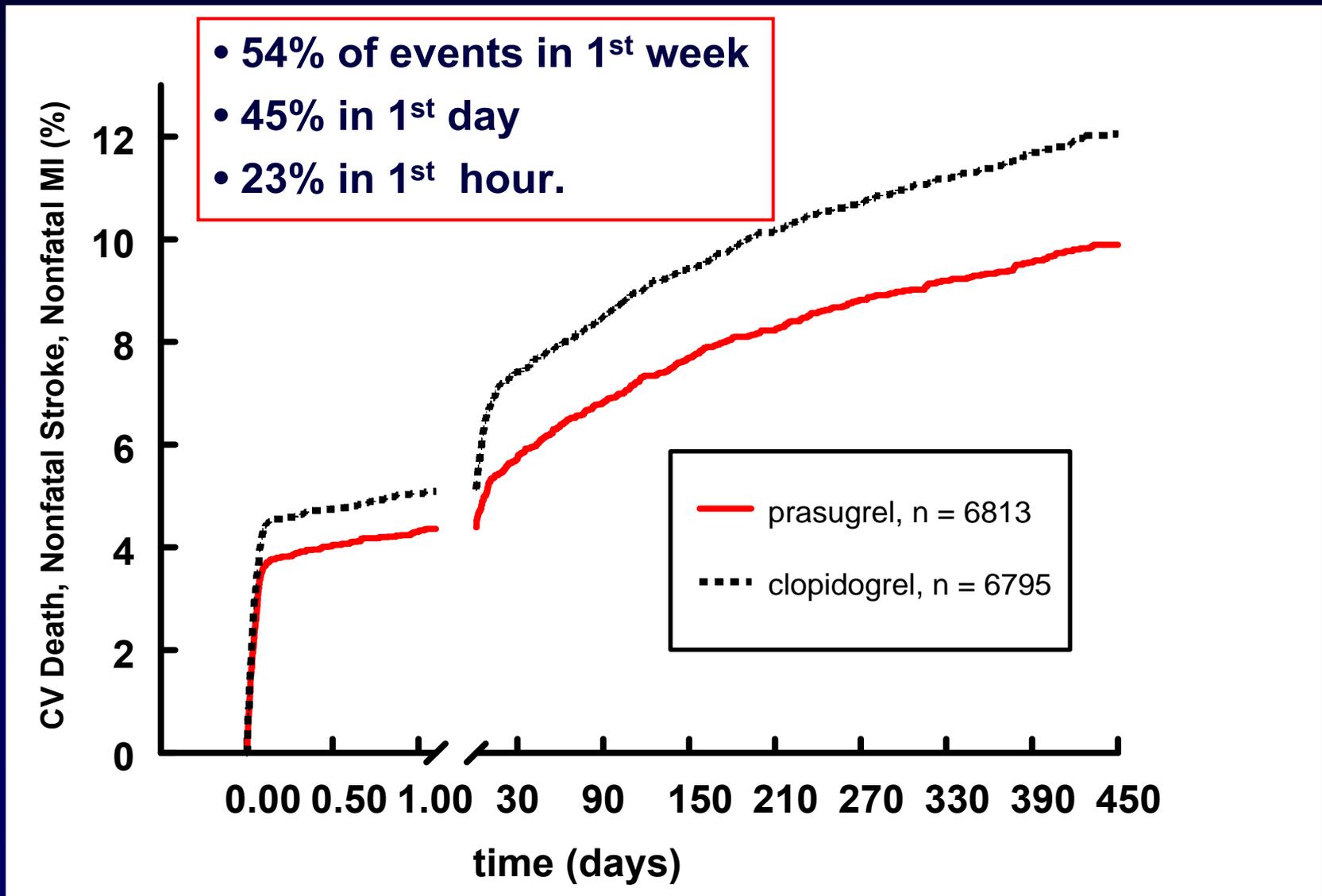
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Endpoint Events are “Front-Loaded” (All ACS):



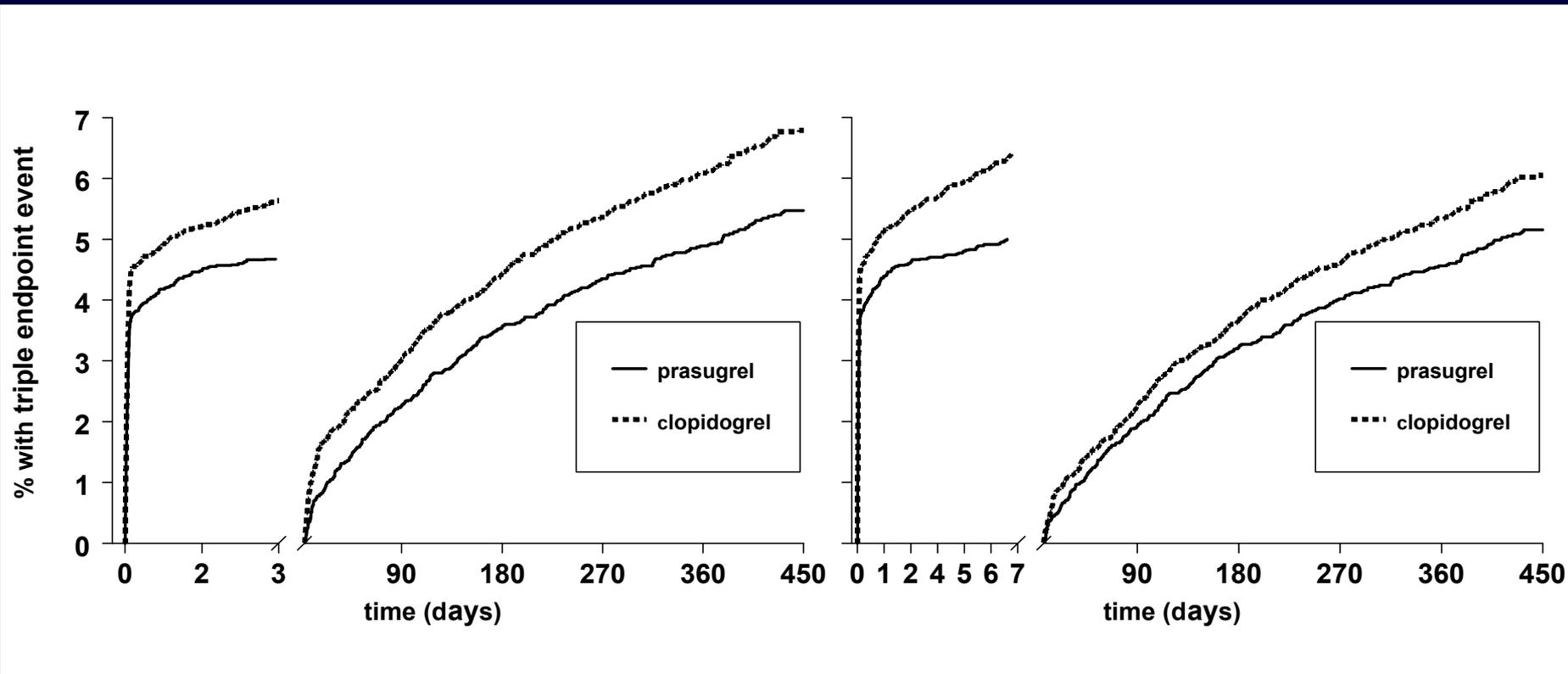
Endpoint Events are “Front-Loaded” (All ACS):



Landmark Analyses on 1° Efficacy Endpoint

All ACS: Days 0-3, 3-450

All ACS: Days 0-7, 7-450

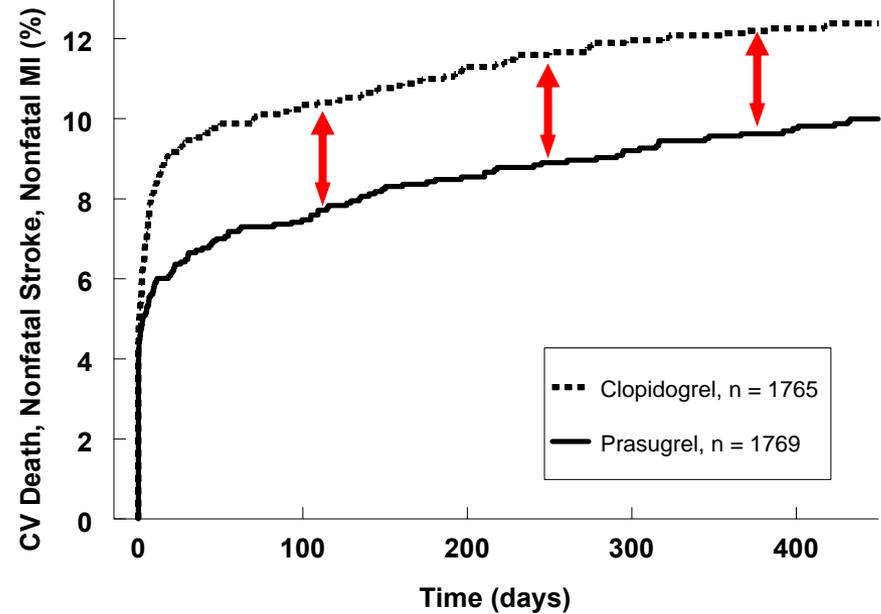
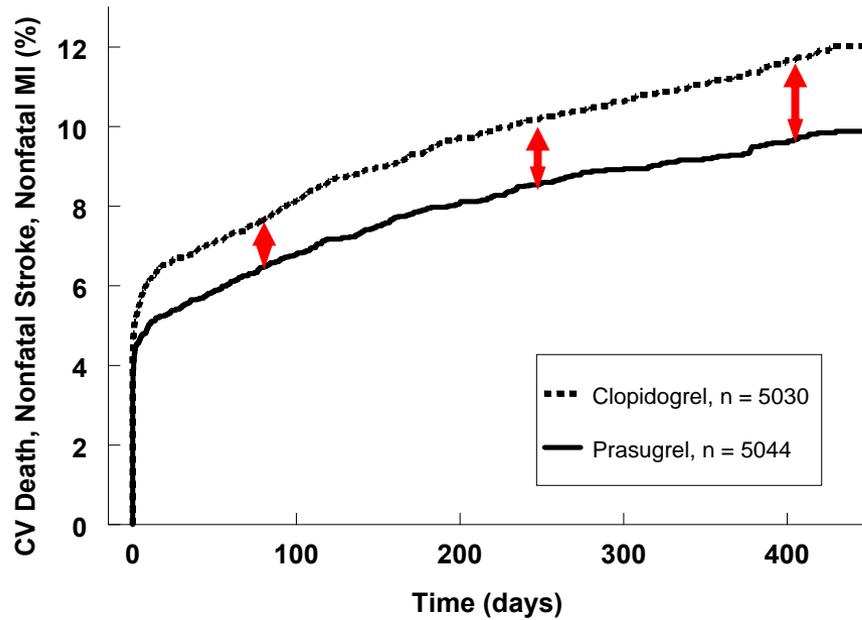


- Results are front-loaded, but landmark analyses argue that superiority is not related solely to loading dose or reduction in peri-procedural MIs

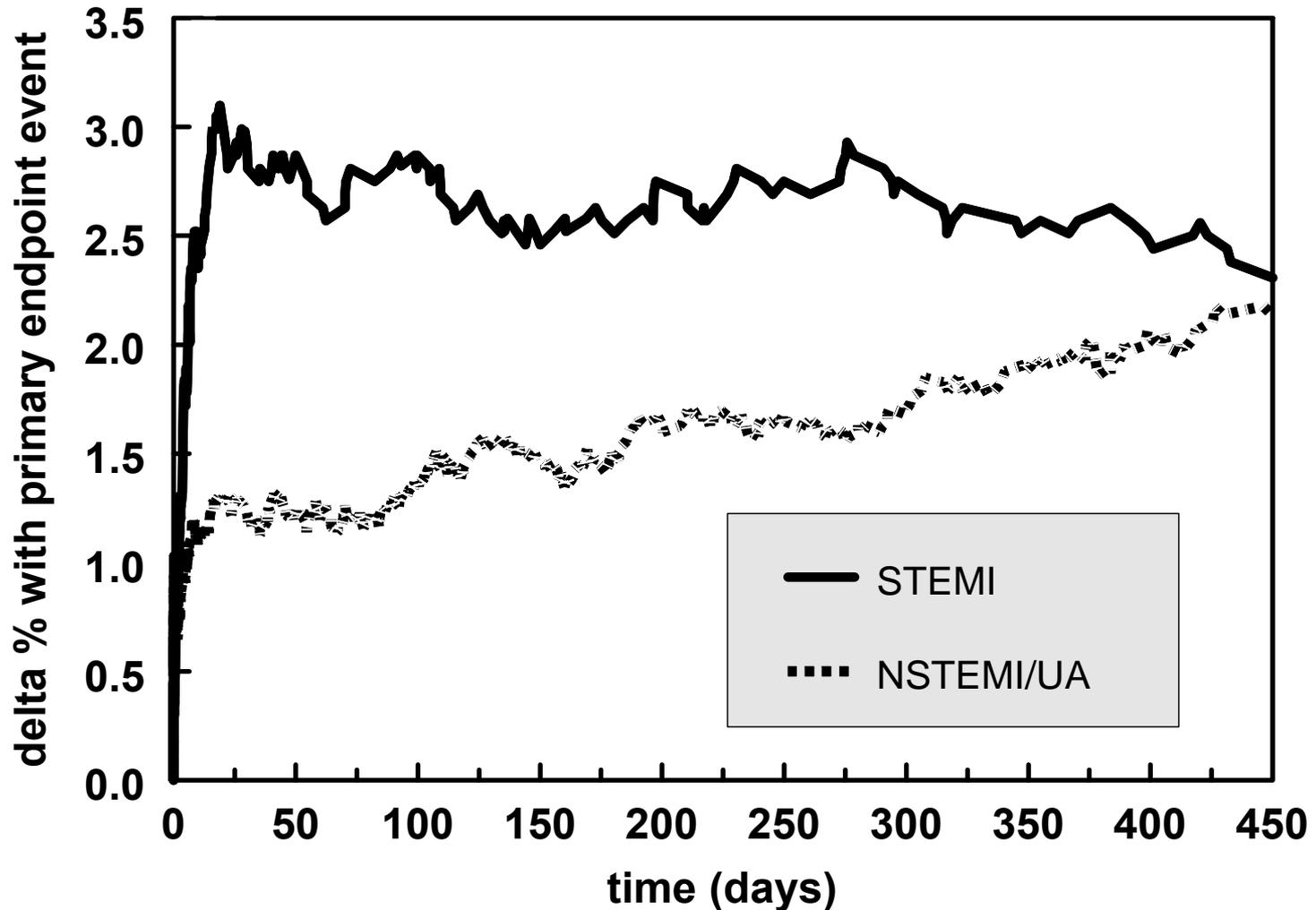
Primary Efficacy Endpoint: Time Course of Development of Treatment Effect

NSTEMI/UA

STEMI

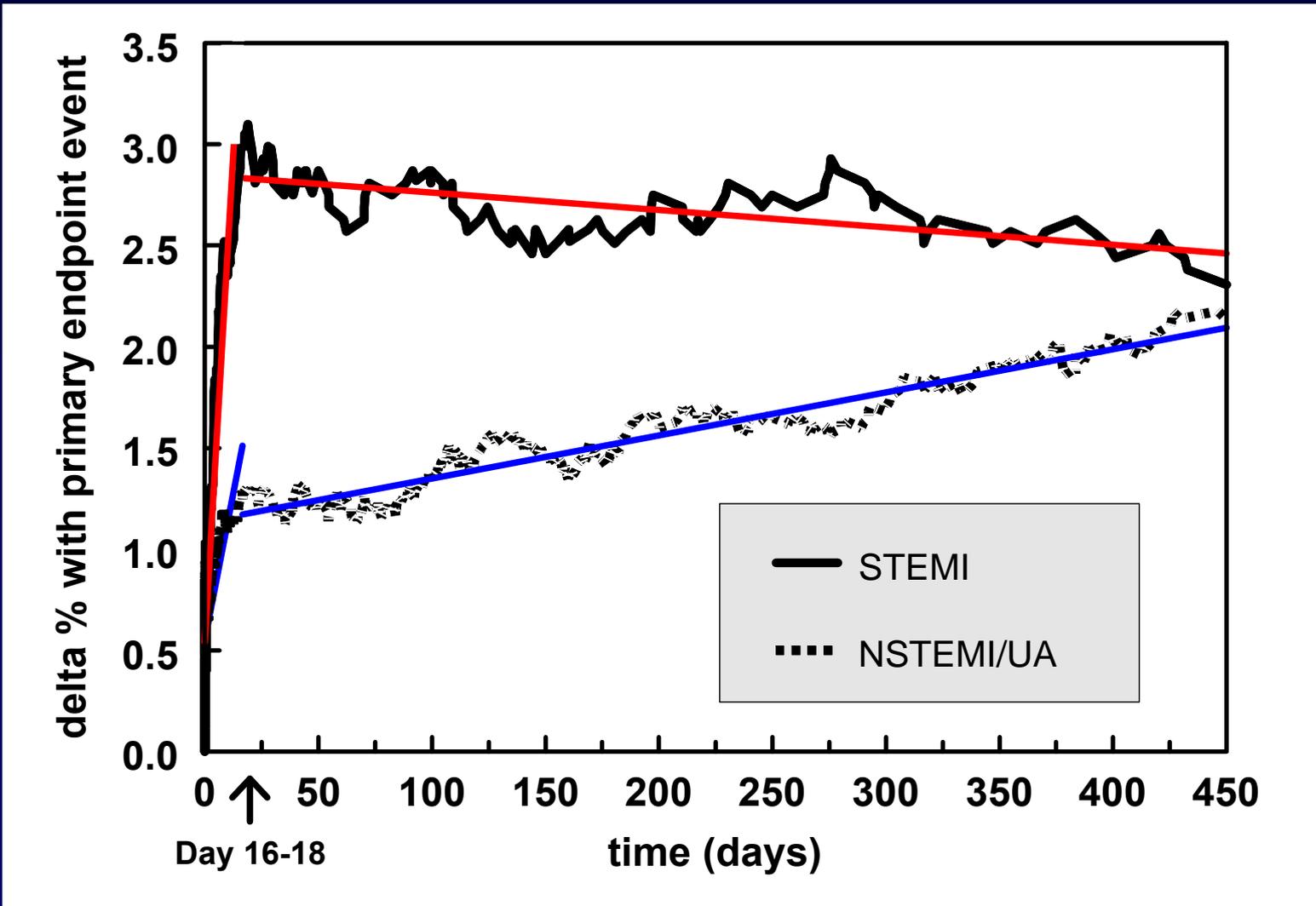


1° Efficacy Endpoint: Delta between Prasugrel and Clopidogrel, STEMI and NSTEMI/UA Populations



1° Efficacy Endpoint:

STEMI – Advantage develops through Day 18, then little change
NSTEMI/UA – Advantage is biphasic, continues through Day 450



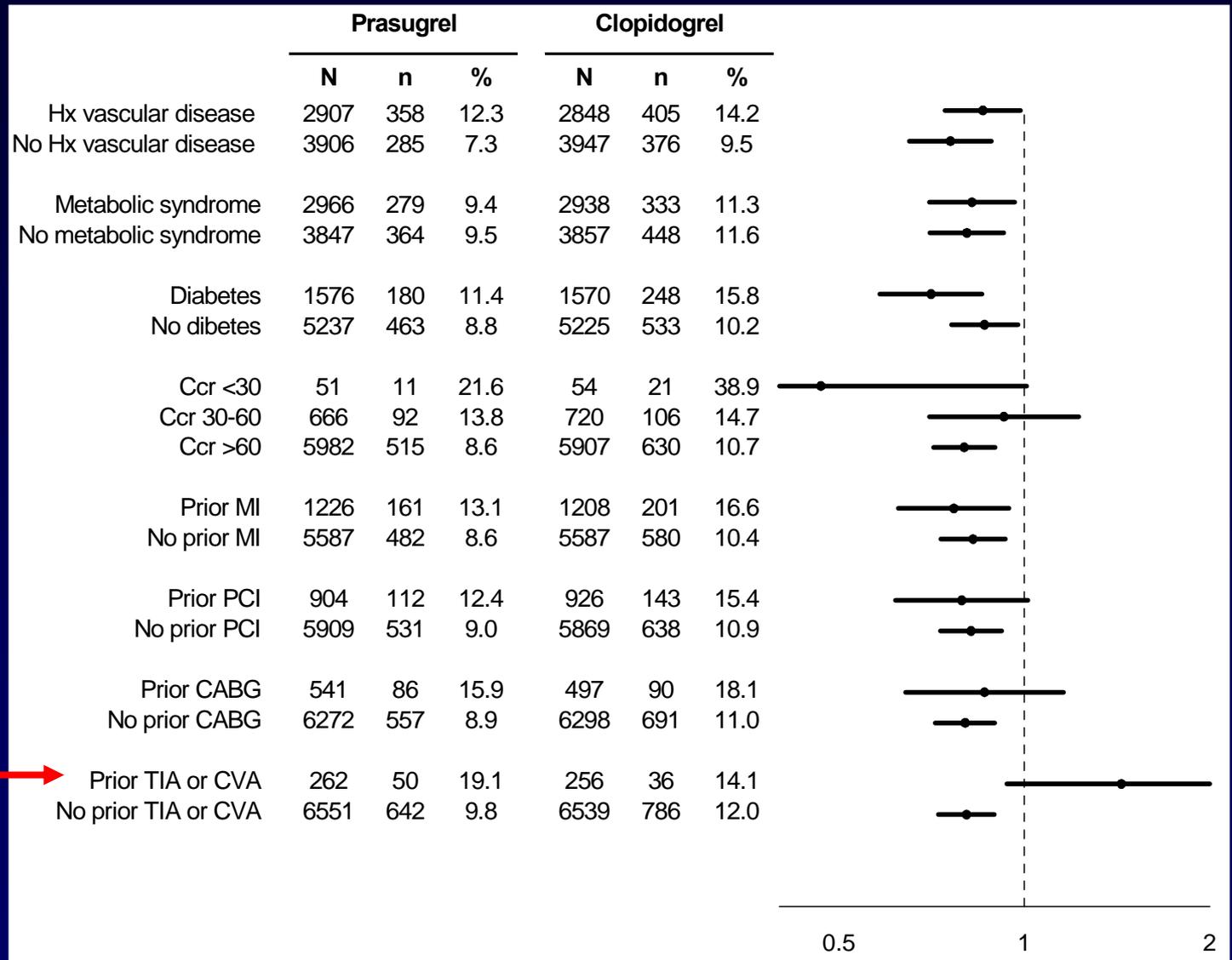
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Subgroup Analyses – Prior Stroke or TIA:

Patients with prior hemorrhagic stroke at any time and non-hemorrhagic stroke <3 months prior to screening were excluded.

Patients with ischemic stroke >3 months prior to screening and patients with prior TIA could be enrolled.



Subgroup Analyses – Patients ≥ 75 :

- Prasugrel's superiority over clopidogrel less certain
- Clopidogrel's superiority over placebo less certain

	Prasugrel			Clopidogrel			HR	95% CI
	N	n	%	N	n	%		
age ≥ 70	1668	235	14.1	1699	257	15.1	<u>0.93</u>	0.78, 1.1
age <70	5145	408	7.9	5096	524	10.3	0.76	0.67, 0.87
age ≥ 75	901	144	16.0	908	154	17.0	<u>0.94</u>	0.75, 1.2
age <75	5912	499	8.4	5887	627	10.7	0.78	0.70, 0.88

CURE - registrational trial for Clopidogrel

	Clopidogrel+ASA		Placebo+ASA		
	%		%		
overall	9.3		11.4		n=12562
age ≥ 75	17.8		19.2		n=2430

Key Concomitant Therapies:

Stents: Hazard ratio for prasugrel compared to clopidogrel – All ACS population:

- Any stent = 0.80 (94% of subjects)
- No stent = 0.67
- Any drug-eluting stent = 0.79
- Any bare metal stent = 0.80

GPIIb/IIIa Inhibitors: Hazard ratio for prasugrel compared to clopidogrel – All ACS population:

- GPIIb/IIIa inhibitor during the index procedure = 0.79 (54% of subjects)
- No GPIIb/IIIa inhibitor during the index procedure = 0.83

Aspirin: No significant interaction

Prasugrel Efficacy: Key Points (1)

- **Large outcome study, n=13,608, 1,424 events (10.5%)**
- **Mean follow up 1 year, median 15 months**
- **Multi-country**
- **Patient management consistent with contemporary practice**
- **Statistically significant reduction in composite endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke (19% relative risk; 2% absolute risk)**
- **Persuasive results across UA/NSTEMI, STEMI, and overall ACS populations**

Prasugrel Efficacy: Key Points (2)

- **Results driven by non-fatal MI, positive trend on mortality, neutral on stroke**
- **Prasugrel's superiority "front-loaded," particularly for STEMI**
- **Positive results across demographic subgroups, concomitant diseases, stent type, GPIIb/IIIa use, and ASA use**
- **Key negative: Patients with prior TIA or non-hemorrhagic stroke did worse on Prasugrel**

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Summary of Deaths in TRITON

	Prasugrel n=6813		Clopidogrel n=6795		Δ events per 1000 patients (positive = favorable for prasugrel)
	n	%	n	%	
	All Cause Death	188	2.76	197	
Cardiovascular (part of 1° endpoint)	133	1.95	150	2.21	2.6
atherosclerotic vascular disease	0	0.00	3	0.04	0.4
CHF/cardiogenic shock	31	0.46	30	0.44	-0.1
related to CABG or PCI	15	0.22	16	0.24	0.2
dysrhythmia	4	0.06	7	0.10	0.4
pulmonary embolism	3	0.04	0	0.00	-0.4
acute MI	24	0.35	36	0.53	1.8
sudden or unwitnessed death	36	0.53	42	0.62	0.9
intracranial hemorrhage (ICH)	9	0.13	5	0.07	-0.6
non-hemorrhagic stroke	5	0.07	6	0.09	0.1
other cardiovascular	6	0.09	5	0.07	-0.1
Non-Cardiovascular	55	0.81	47	0.69	-1.2
accident/trauma	4	0.06	4	0.06	0.0
* hemorrhage, extra-cranial	9	0.13	1	0.01	-1.2
infection	11	0.16	10	0.15	-0.1
malignancy	21	0.31	17	0.25	-0.6
suicide	3	0.04	2	0.03	-0.1
other	7	0.10	13	0.19	0.9

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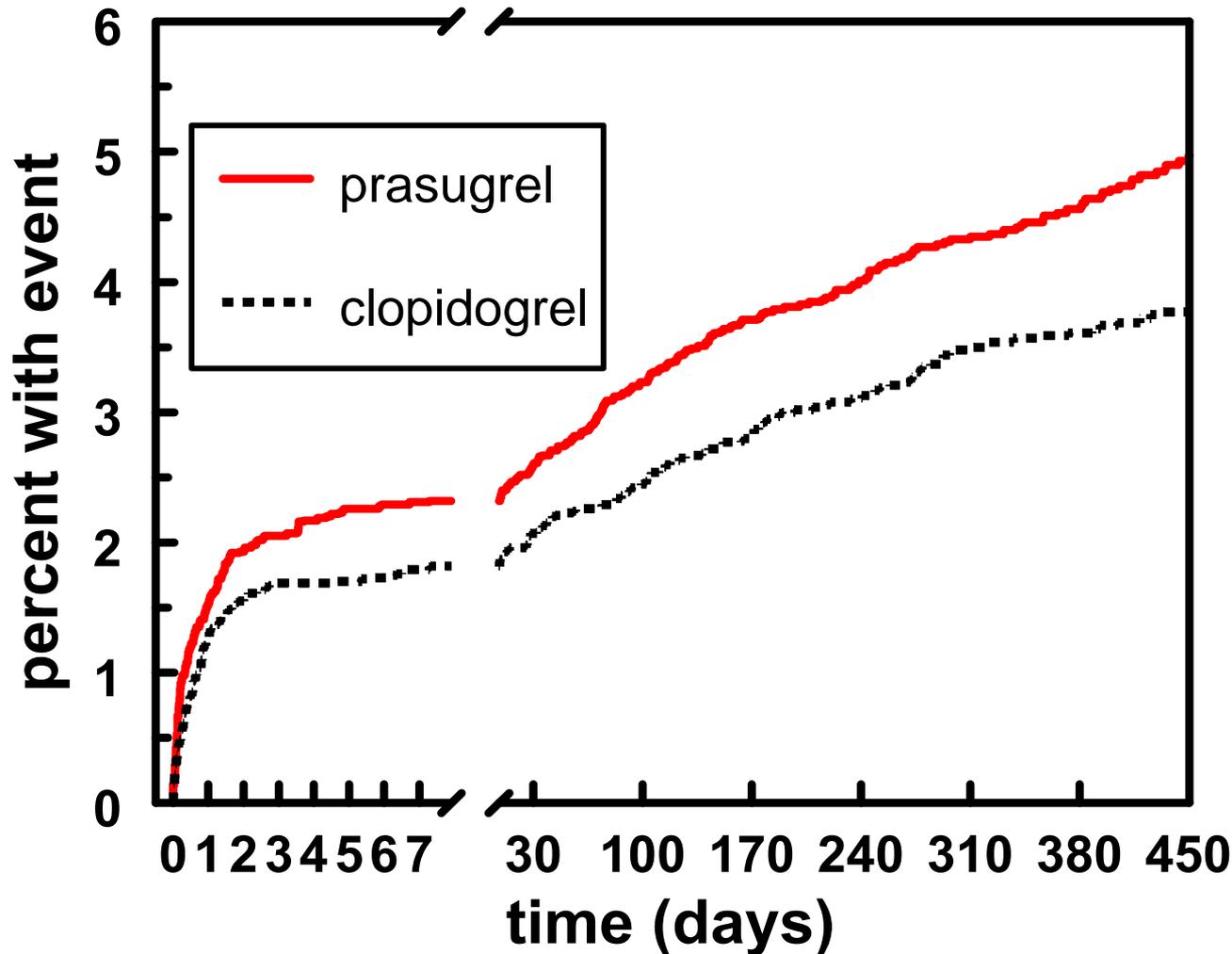
Bleeding Definitions in TRITON

- **TIMI Major Bleed** \equiv any intracranial hemorrhage, or overt bleeding requiring intervention associated with a decrease in hemoglobin ≥ 5 g/dL
- **TIMI Minor bleeding** \equiv clinically overt bleeding associated with a decrease in hemoglobin of ≥ 3 g/dL but < 5 g/dL
- **Bleeding was categorized as related to, or not related to, coronary artery bypass graft (CABG) surgery.**

Adjudicated Bleeding by TIMI Classification

<u>TIMI Bleeding</u>	<u>Prasugrel</u>			<u>Clopidogrel</u>			<u>HR (95% C.I.)</u>
<u>Non-CABG-Related:</u>	<u>N</u>	<u>n</u>	<u>%</u>	<u>N</u>	<u>n</u>	<u>%</u>	
<u>Fatal</u>	<u>6741</u>	<u>21</u>	<u>0.3</u>	<u>6716</u>	<u>5</u>	<u>0.1</u>	<u>4.19 (1.58, 11.1)</u>
<u>Life-threatening</u>	<u>6741</u>	<u>85</u>	<u>1.3</u>	<u>6716</u>	<u>56</u>	<u>0.8</u>	<u>1.52 (1.08, 2.13)</u>
<u>Major</u>	<u>6741</u>	<u>146</u>	<u>2.2</u>	<u>6716</u>	<u>111</u>	<u>1.7</u>	<u>1.32 (1.03, 1.68)</u>
<u>Minor</u>	<u>6741</u>	<u>164</u>	<u>2.4</u>	<u>6716</u>	<u>125</u>	<u>1.9</u>	<u>1.31 (1.04, 1.66)</u>
<u>Minimal</u>	<u>6741</u>	<u>460</u>	<u>6.8</u>	<u>6716</u>	<u>314</u>	<u>4.7</u>	<u>1.47 (1.28, 1.70)</u>
<u>CABG-Related:</u>							
<u>Fatal</u>	<u>213</u>	<u>2</u>	<u>0.9</u>	<u>224</u>	<u>0</u>	<u>0.0</u>	
<u>Major</u>	<u>213</u>	<u>24</u>	<u>11.3</u>	<u>224</u>	<u>8</u>	<u>3.6</u>	<u>3.50 (1.53, 7.99)</u>
<u>*All Fatal:</u>	<u>6954</u>	<u>23</u>	<u>0.3</u>	<u>6940</u>	<u>5</u>	<u>0.1</u>	<u>4.59 (1.75, 12.1)</u>

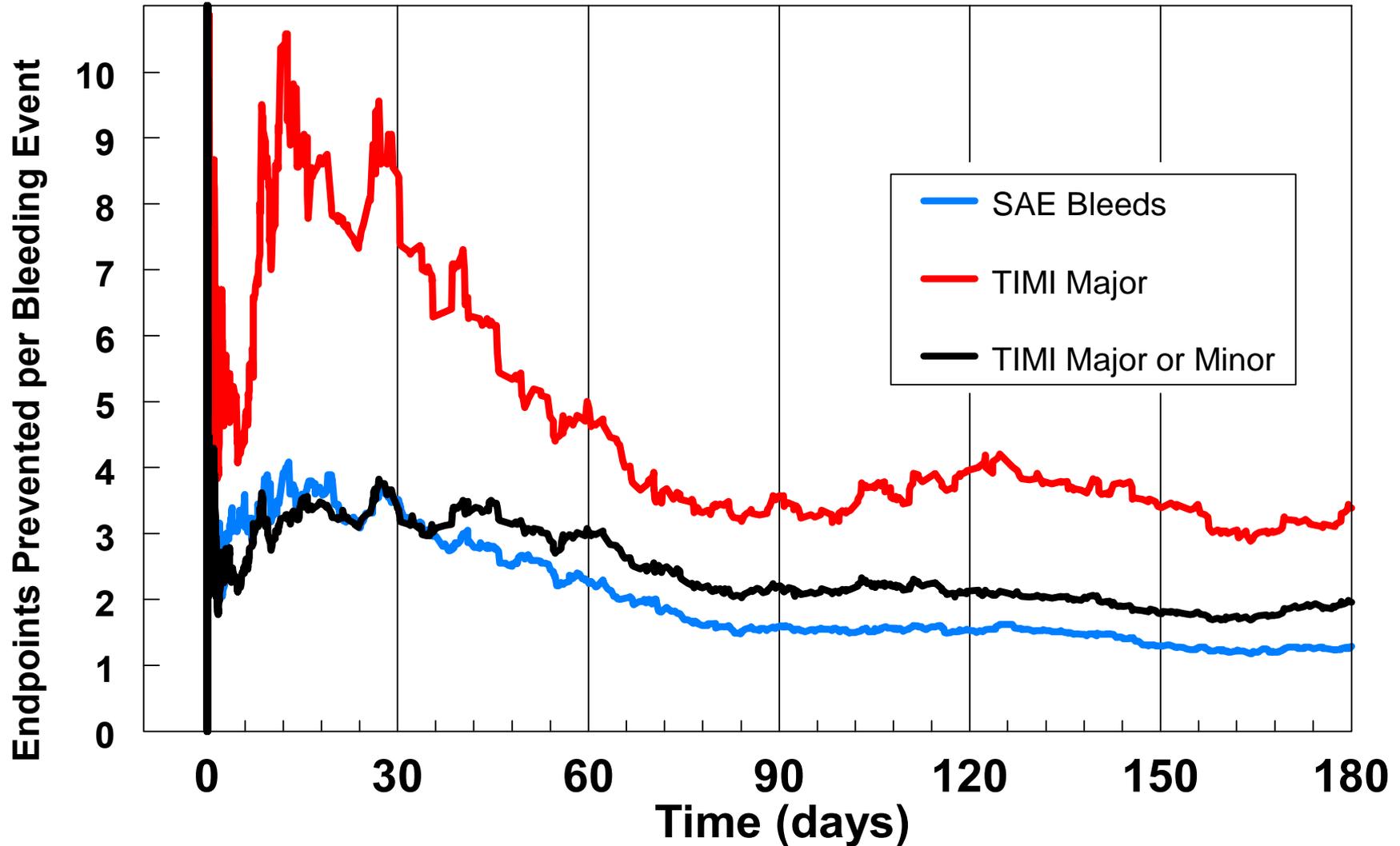
Non-CABG-Related TIMI Major or TIMI Minor Bleeding Events – All ACS Population



Bleeds were front-loaded:

- Approximately 1/3 of all bleeds were reported on the first day.
- Nearly half of all bleeds were reported within the initial 7 days.

Cumulative Benefit-Risk of Prasugrel Compared to Clopidogrel by Time: All ACS Population

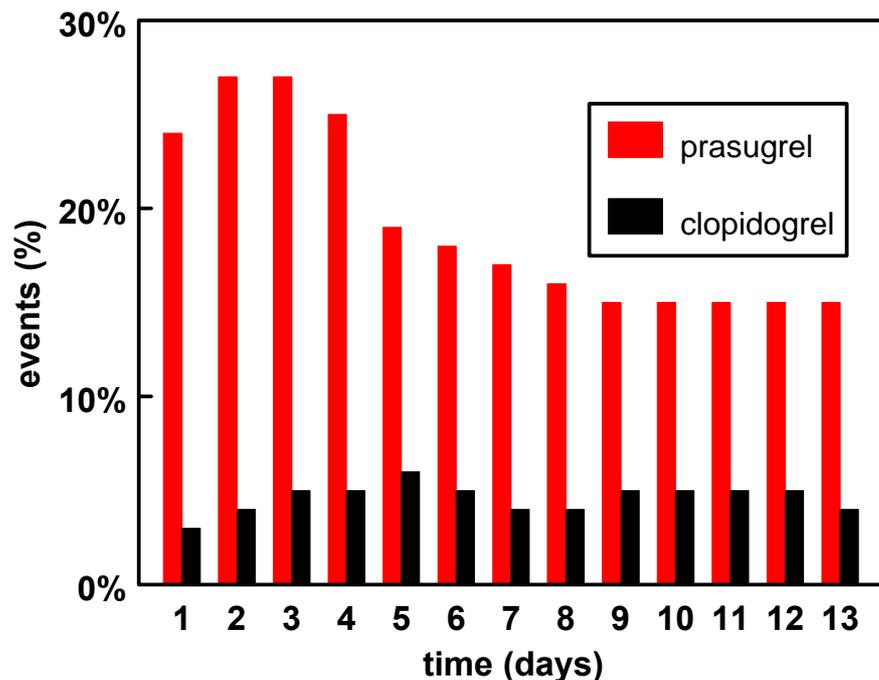


CABG-Related TIMI Major or Minor Bleeding Events: Days from Last Dose of Study Drug to CABG

Days from last dose to CABG	Prasugrel			Clopidogrel		
	N	n	%	N	n	%
0	12	1	8.3	22	1	4.5
1	17	6	35.3	12	0	0
2	4	2	50	11	1	9.1
3	12	3	25	15	1	6.7
4	8	1	12.5	14	1	7.1
5	30	3	10	30	2	6.7
6	18	2	11.1	21	0	0
7	24	3	12.5	25	0	0
8	13	1	7.7	10	0	0
9	8	0	0	9	2	22.2
10	10	2	20	5	0	0
11	5	0	0	2	0	0
12	3	0	0	1	0	0
13	1	1	100	2	0	0
14-27	9	0	0	11	0	0
28	1	1	100	1	0	0
29-60	4	0	0	3	0	0
61-341	6	1	16.7	5	0	0

N = numbers of subjects who underwent CABG
n = numbers of bleeding events

Cumulative frequency



TIMI Major or Minor Bleeding and Patient Weight:

weight quintile	weight range	Prasugrel			Clopidogrel			RR
		N	n	%	N	n	%	
overall	all	6741	303	4.5	6716	231	3.4	1.31
1	(32 - 70)	1416	96	6.8	1526	75	4.9	1.38
2	(>70 - 78)	1265	61	4.8	1245	43	3.5	1.40
3	(>78 - 85)	1365	49	3.6	1315	39	3.0	1.21
4	(>85 - 95.2)	1291	50	3.9	1265	42	3.3	1.17
5	(>95.2)	1344	43	3.2	1304	30	2.3	1.39
weight unknown		60	4	6.7	61	2	3.3	2.03
weight ≤ 60 kg *		412	40	9.7	444	25	5.6	1.72

* Weight ≤ 60 kg is a subset of quintile #1.

- Patients in quintile #1 (≤ 70 kg) not at particularly high relative risk.
- Patients ≤ 60 kg at higher relative risk, but small subset.

TIMI Major or Minor Bleeding and Patient Age:

age	Prasugrel			Clopidogrel			RR
	N	n	%	N	n	%	
overall	6741	303	4.5	6716	231	3.4	1.31
<65	4149	141	3.4	4096	99	2.4	1.41
>=65	2592	162	6.3	2620	132	5.0	1.26
<70	5095	182	3.6	5041	138	2.7	1.31
>=70	1646	121	7.4	1675	93	5.6	1.35
<75	5850	223	3.8	5822	169	2.9	1.32
>=75	891	80	9.0	894	62	6.9	1.35

- Patients over 70 not at particularly high RR of bleeding; however, prasugrel's bleeding was malignant in outcome:
- **Fatal hemorrhage: 9/891 (1.0%) for prasugrel vs. 1/894 (0.1%) for clopidogrel.**
- **Symptomatic ICH: 7/891 (0.8%) vs. 3/894 (0.3%), respectively.**

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Does Prasugrel Cause Cancer?

- Genetic toxicology studies negative
- Time course of events observed in TRITON is not consistent with carcinogenesis

**Conclusion: There is no evidence that Prasugrel causes cancer.
Carcinogenesis is not an issue.**

Could Prasugrel Stimulate Tumors?

- **Time course of discovery of new cancers and worsening of existing cancers in TRITON could be consistent with tumor stimulation.**

Could Prasugrel Stimulate Tumors? Yes, but:

- This phenomenon is rare; has been observed with drugs known to stimulate tissue growth
- Cell culture studies, recently completed, appear negative, though still under FDA review. Prasugrel:
 - Did not increase cell proliferation relative to starved cells stimulated by addition of 10% fetal bovine serum (FBS)
 - Had no effect on human tumor xenografts (lung, colon, prostate) *in vivo*
- Effect through platelets plausible, but no effect of clopidogrel when compared to placebo in CURE, CAPRIE, and CHARISMA

Imbalance in Neoplasia: Non-Clinical Studies

- **24-month carcinogenicity study in rats:**
 - **Diffuse hepatocyte hypertrophy**
 - **No dose-response in excess tumors**
 - **No evidence of malignant tumors in the 2-year lifetime study**
- **24-month carcinogenicity study in mice:**
 - **Statistically significant increase in hepatocellular adenoma (dose-related)**
 - **Trend for hepatocellular carcinomas, not statistically significant, identified by one member of review team**

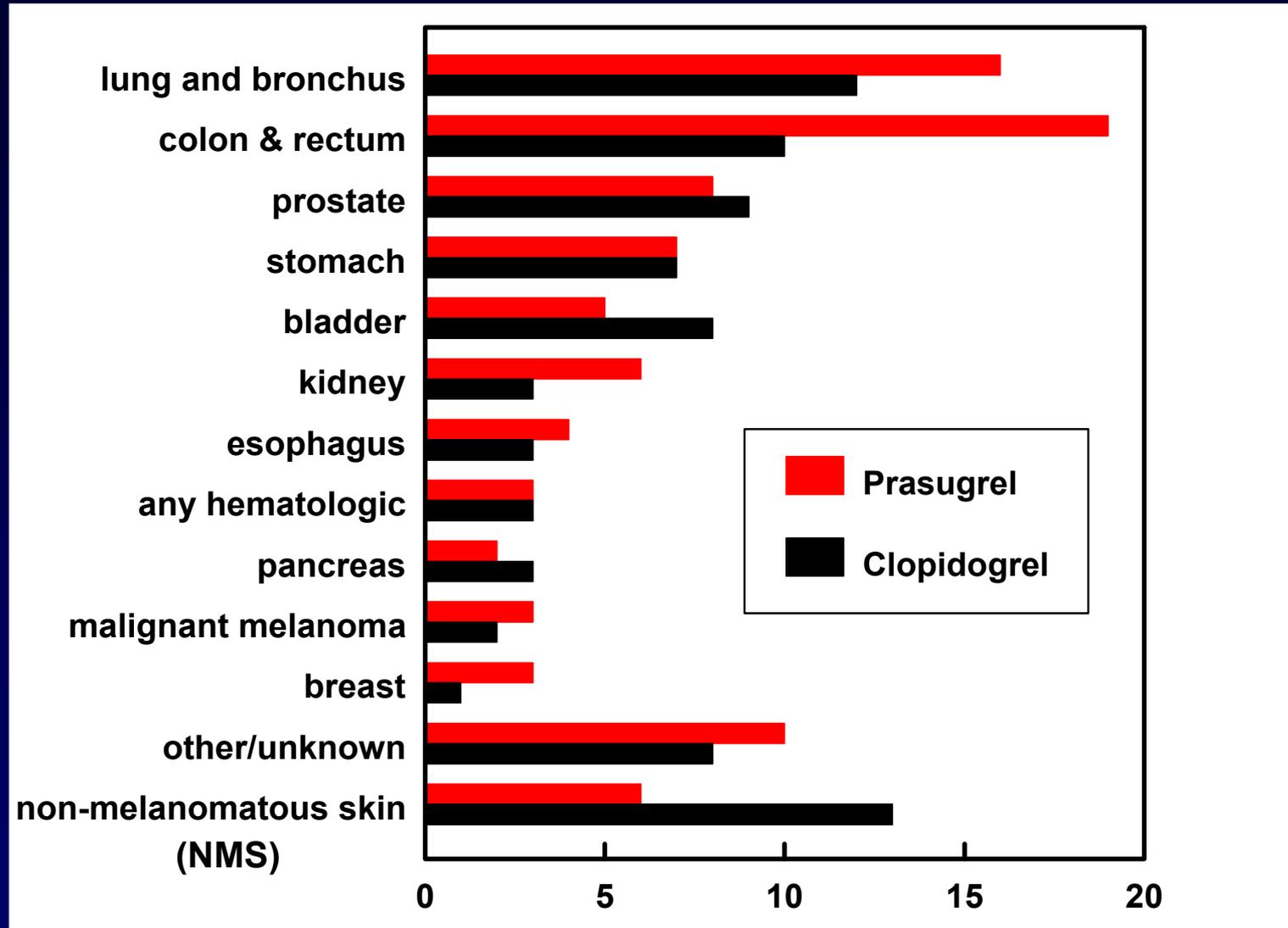
Neoplasia in TRITON: Weaknesses in Data

- No baseline cancer screening
- Investigators were to “...list all **ongoing** medical conditions at the time of study entry/screening.”
 - “Ongoing” ambiguous, subject to interpretation
 - Uncertain attention paid to past medical history for patients in the throes of ACS
- Rarely, prior medical historical data were deleted, replaced by adverse events
- Analyses post hoc, unblinded

Neoplasia in TRITON: Some Background

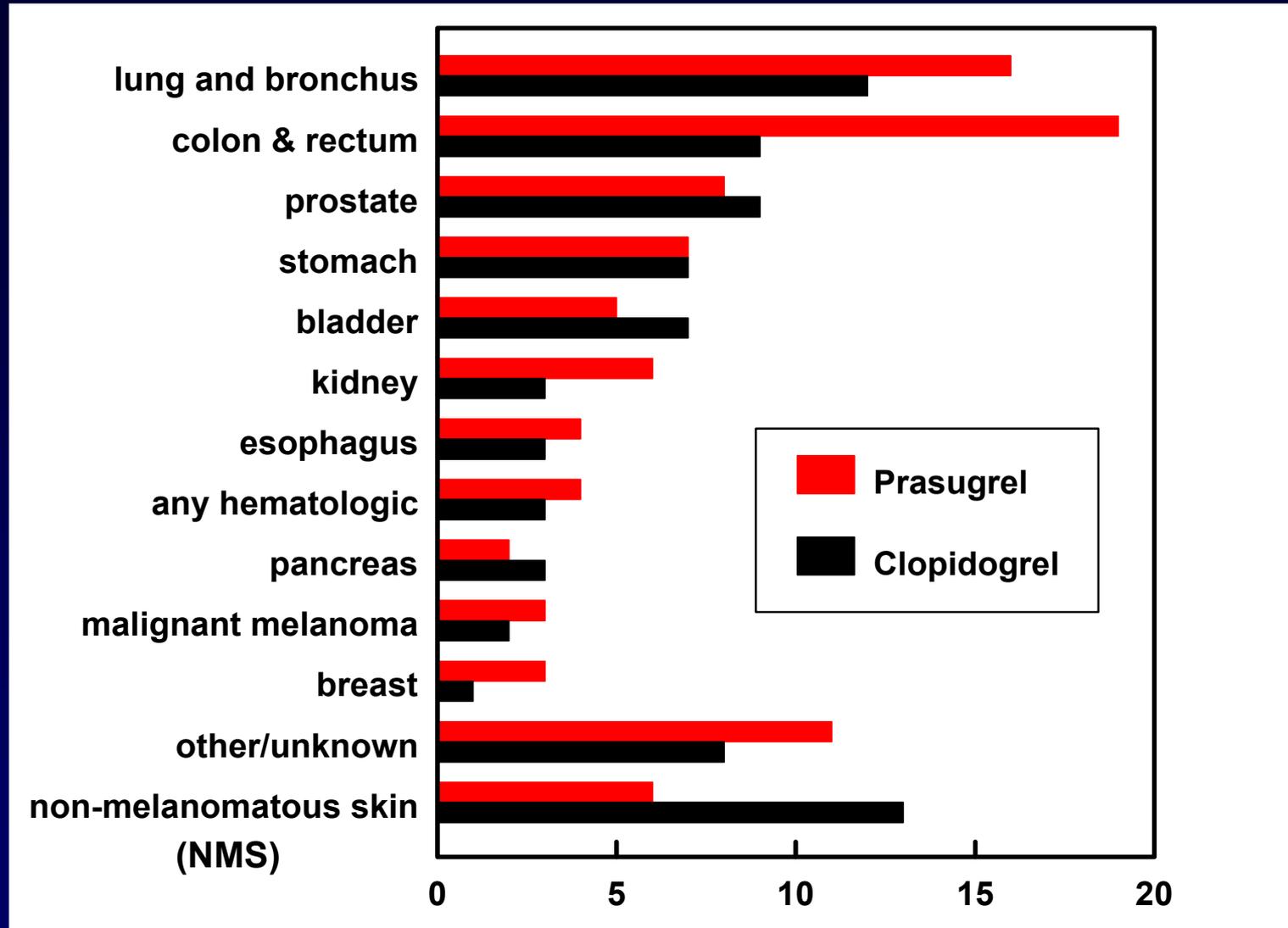
- At baseline, frequency of “pre-existing” malignancies was 2.6% in both treatment groups
- Non-melanomatous skin (NMS) cancers lack clinical importance of most solid tumors:
 - Relatively common
 - Readily cured by excision
 - Largely ignored in cancer statistics
- But – NMS cancers are malignancies
 - Should be considered in terms of tumor stimulation
 - Less important from public health standpoint

TRITON: Imbalance in Neoplasia



Original classification: include all: RR=1.17; 95% CI 0.87, 1.57
exclude NMS: RR=1.31; 95% CI 0.95, 1.79

TRITON: Imbalance in Neoplasia



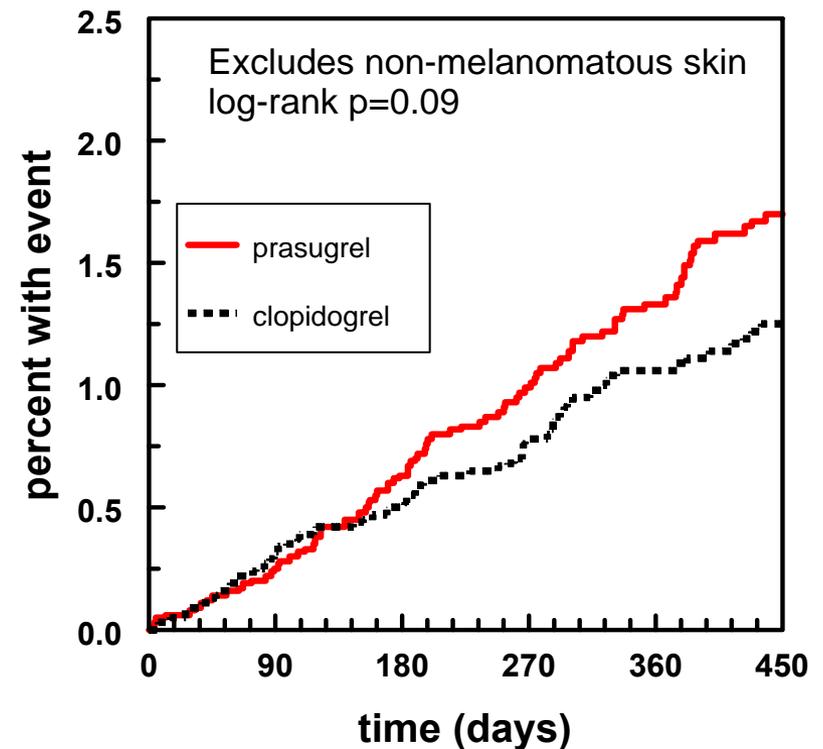
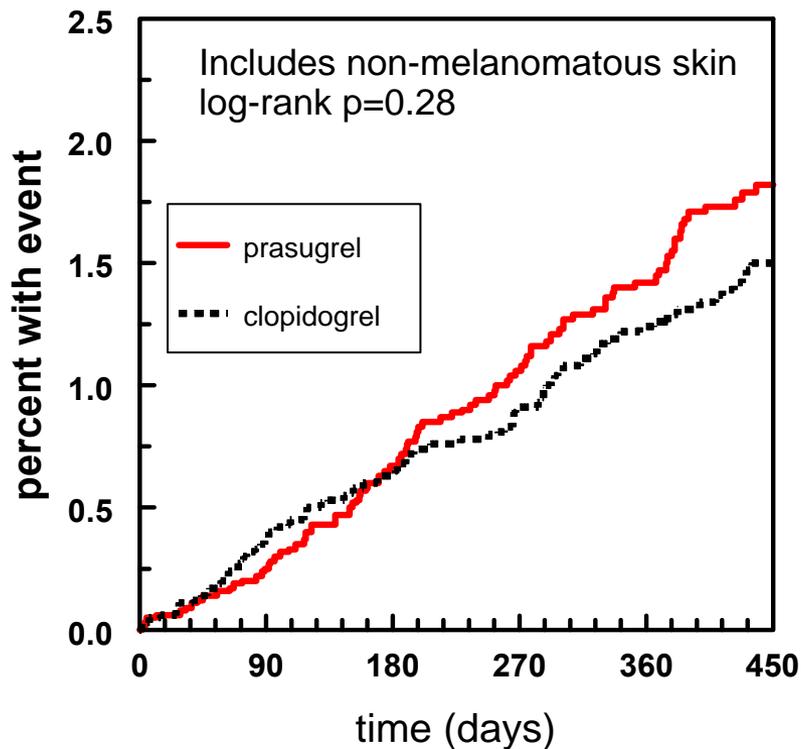
Reclassify 4 cases: include all: RR=1.23; 95% CI 0.91, 1.65
exclude NMS: RR=1.38; 95% CI 1.00, 1.89, p<0.05

New, Non-Benign Neoplasms

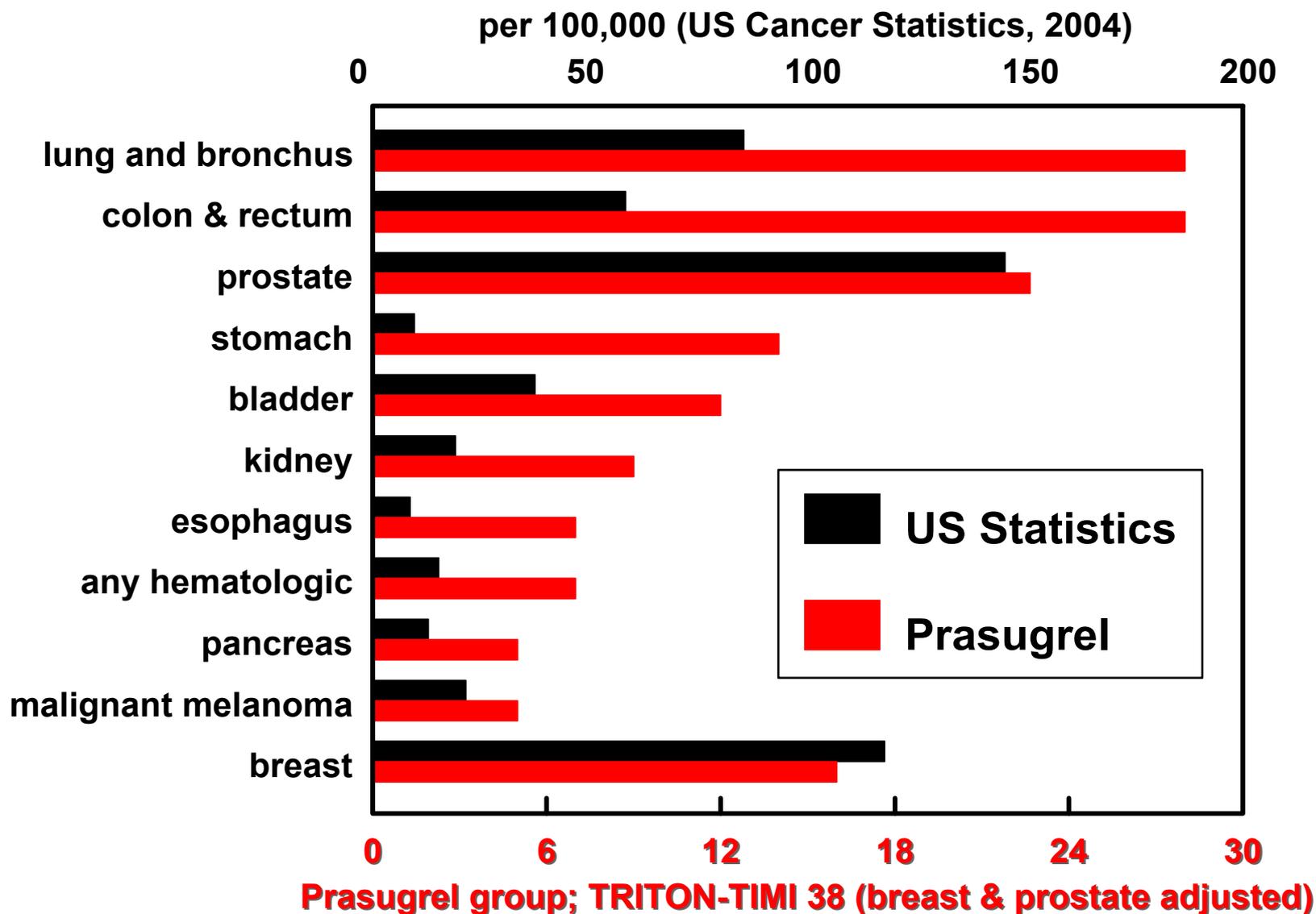
Non-melanomatous skin:

include

exclude



Neoplasms in TRITON vs. US Population



Imbalance in Neoplasia: Ascertainment Bias?

	Prasugrel (n=6741)		Clopidogrel (n=6716)		RR
	n	%	n	%	
Gastrointestinal (colorectal/esophagus/stomach)					
total	32	0.47	19	0.28	1.7
with bleed	25	0.4	14	0.2	1.8
without bleed	7	0.1	5	0.1	1.4
Genitourinary (kidney and urethral/bladder/gynecologic)					
total	13	0.2	12	0.2	1.1
with bleed	7	0.1	8	0.1	0.9
without bleed	6	0.1	4	0.1	1.5
Respiratory (lung/bronchus)					
total	16	0.2	13	0.2	1.2
with bleed	3	0.0	3	0.0	1.0
without bleed	13	0.2	10	0.1	1.3
All 3 Systems:					
total	61	0.9	44	0.7	1.4
with bleed	35	0.5	25	0.4	1.4
without bleed	26	0.4	19	0.3	1.4

- **Bleeding led to cancer diagnoses, but did not account for imbalance between treatment groups.**

Malignancy Deaths in TRITON:

Table 8. Vital Status of Subjects With a Pre-existing Non-Benign Neoplasm

			Pras	Clop
Total			28	10
Vital Status	Primary Cause of Death	Subcategory		
ALIVE			17	6
DEAD	CARDIOVASCULAR		1	0
	NON-CARDIOVASCULAR	MALIGNANCY	6	2
		OTHER	0	1
	UNKNOWN CAUSE		1	1
TOTAL DEAD			8	4
UNKNOWN			3	0

Source: l0463_fqvitj11_vital.rtf

Total malignancy deaths:

**Prasugrel = 33;
Clopidogrel = 21**

RR = 1.57

- Imbalance in deaths is concerning.**

- For death, we expect 100% ascertainment, without bias.**

Table 14. Vital Status of Subjects With a New Non-Benign Neoplasm

			Pras	Clop
Total			100	84
Vital Status	Primary Cause of Death	Subcategory		
ALIVE			58	54
DEAD	CARDIOVASCULAR		1	3
	NON-CARDIOVASCULAR	MALIGNANCY	27	19
		OTHER	6	2
	UNKNOWN CAUSE		1	1
TOTAL DEAD			35	25
UNKNOWN			7	5

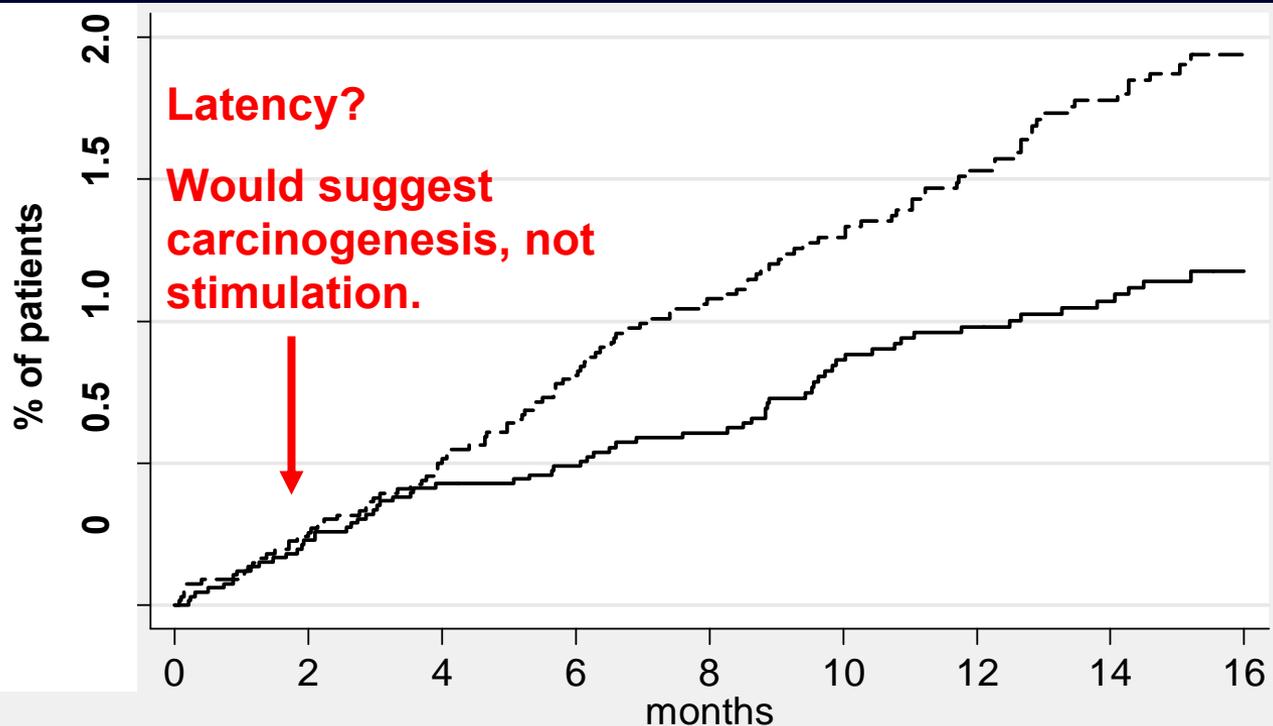
Source: l0463_fqvitj11_vital.rtf

“Worse” Neoplasms

30 Subjects:

- Required cancer surgery, n=12**
- Died of cancer, n=7**
- Developed metastases, n=4**
- Cancer recurred, n=3**
- Adverse event for worsening cancer, n=2**
- Received radiation therapy, n=2**

New and Worse Solid Neoplasms



Number at risk		0	2	4	6	8	10	12	14	16
rx = Clopidogrel	6795	6511	6445	6341	5784	5131	4809	4301	505	
rx = Prasugrel	6813	6557	6463	6344	5728	5099	4749	4228	491	

— rx = Clopidogrel - - - - rx = Prasugrel

- Excludes non-melanomatous skin cancers and brain tumors; **p=0.001**

Neoplasia: Reasons for Reassurance and Concern

Reassurance:

- **Non-clinical data negative**
- **No putative mechanism of action**
- **Multiplicity of safety analyses – potential for false positive finding**
- **From mechanistic standpoint, no reason to exclude non-melanomatous skin cancer; signal largely disappears if all skin included**

Neoplasia: Reasons for Reassurance and Concern

Concerns:

- **Excess malignancy deaths are concerning, cannot be explained by bias**
- **Risk of cancer would seem to be continuous during therapy, whereas benefit is largely front-loaded**

Prasugrel: Points for Discussion

- **Efficacy**
 - Time course
 - Subgroups with marginal effectiveness
- **Safety**
 - Deaths
 - Bleeding
 - Subgroups at particular risk
 - Neoplasia
- **Quality**
 - Form conversion from salt to base

History: Salt to Base Form Conversion

- **Development initiated using the free base form of prasugrel drug substance**
- **Sponsor became aware that salt form had better bioavailability at higher gastric pH**
- **Manufacturing process altered to produce salt form**
- **Late in development, the sponsor discovered form conversion from the salt to the base ranging from 42% to 87% base content in tablet batches used in TRITON.**

Salt to Base Form Conversion – Why Do We Care?

21 CFR 314.125(b)(1)

PART 314 -- Applications for FDA approval to market a new drug

Subpart D--FDA Action on Applications and Abbreviated Applications

Sec. 314.125 Refusal to approve an application.

b) FDA may refuse to approve an application for any of the following reasons:

1) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.

Assessment: Salt to Base Form Conversion

- **Pharmacokinetics**
 - **Prasugrel is a pro-drug (not readily measurable)**
 - **Active moiety is R-138727 (measurable)**
- **Pharmacodynamics**
 - **Effects on inhibition of platelet aggregation**

Pharmacokinetics: Salt to Base Form Conversion

Relative Bioavailability of R-138727 (active moiety of prasugrel)

- Lots with low (5%), medium (58%), and high (70%) conversion, 60-mg loading dose
- Bioavailability pH-dependent:
 - In absence of proton pump inhibitor (PPI)
 - In presence of PPI (background lansoprazole)

Pharmacokinetics: Salt to Base Form Conversion

In absence of proton pump inhibitor (PPI):

- **Prasugrel lots with low (5%), medium (58%), and high (70%) conversion are bioequivalent.**

Pharmacokinetics: Salt to Base Form Conversion

In presence of proton pump inhibitor (PPI):

- **Prasugrel lots with low (5%), medium (58%), and high (70%) conversion are:**
 - bioequivalent with respect to area under the curve (AUC);
 - - bioinequivalent with respect to C_{max} .

Pharmacokinetics: Salt to Base Form Conversion

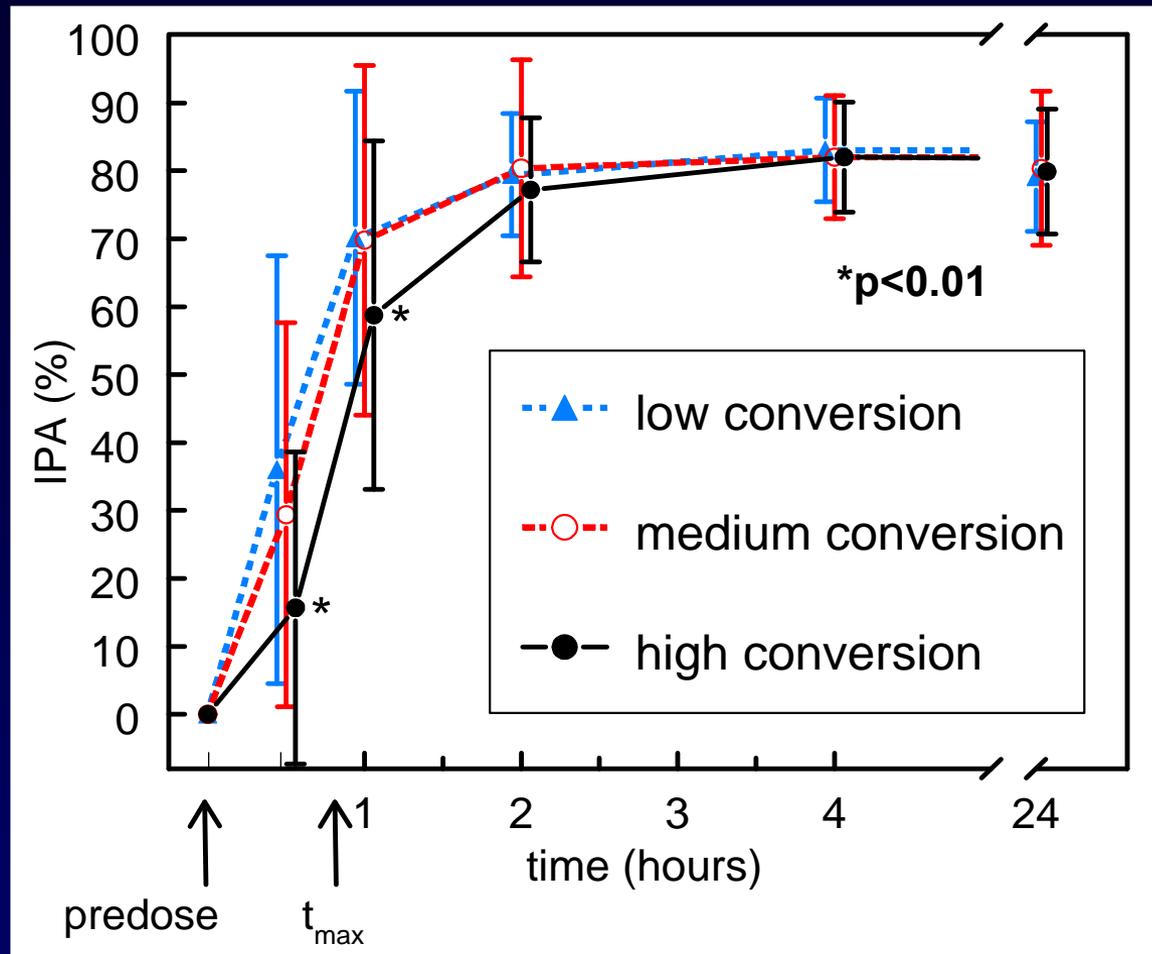
- In presence of PPI: 60-mg Prasugrel is bioinequivalent with respect to C_{max}:**

	Ratio of means (90% CI)		
	medium conversion/ low conversion	high conversion/ low conversion	high conversion/ medium conversion
AUC(0-t_{last}) (ng•h/mL)	0.99 (0.93, 1.06)	0.87 (0.82, 0.93)	0.88 (0.82, 0.93)
C_{max} (ng/mL)	0.90 (0.77, 1.04)	0.71 (0.62, 0.83)	0.80 (0.69, 0.92)

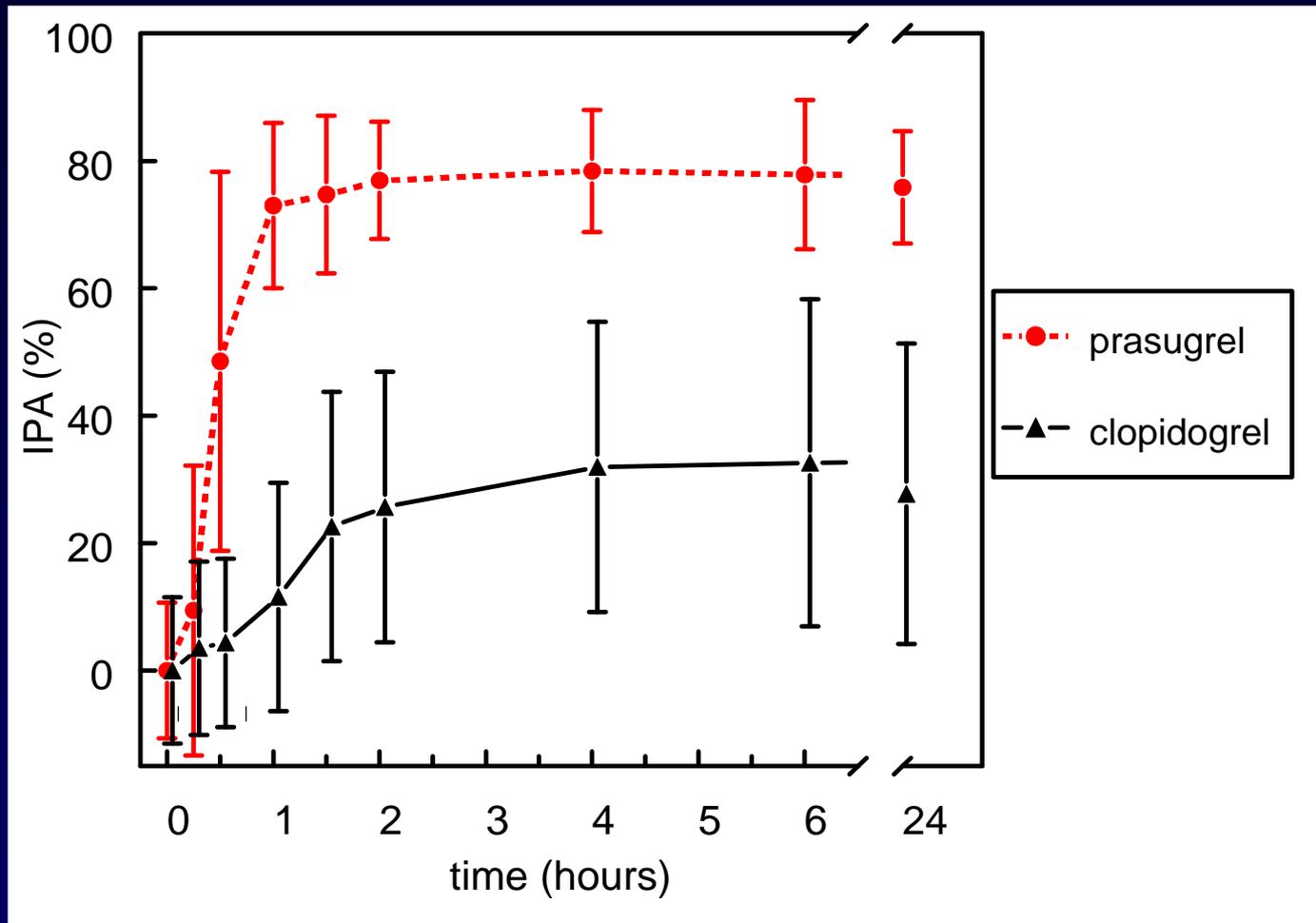
- 90% CI is not within 80-125%.**

Pharmacodynamics: Salt to Base Form Conversion, Study TACS

- In presence of PPI: delayed inhibition of platelet aggregation (IPA) with high conversion lot
- This would affect loading dose, close to time of initial administration (? early efficacy and safety)
- No effect on maintenance doses

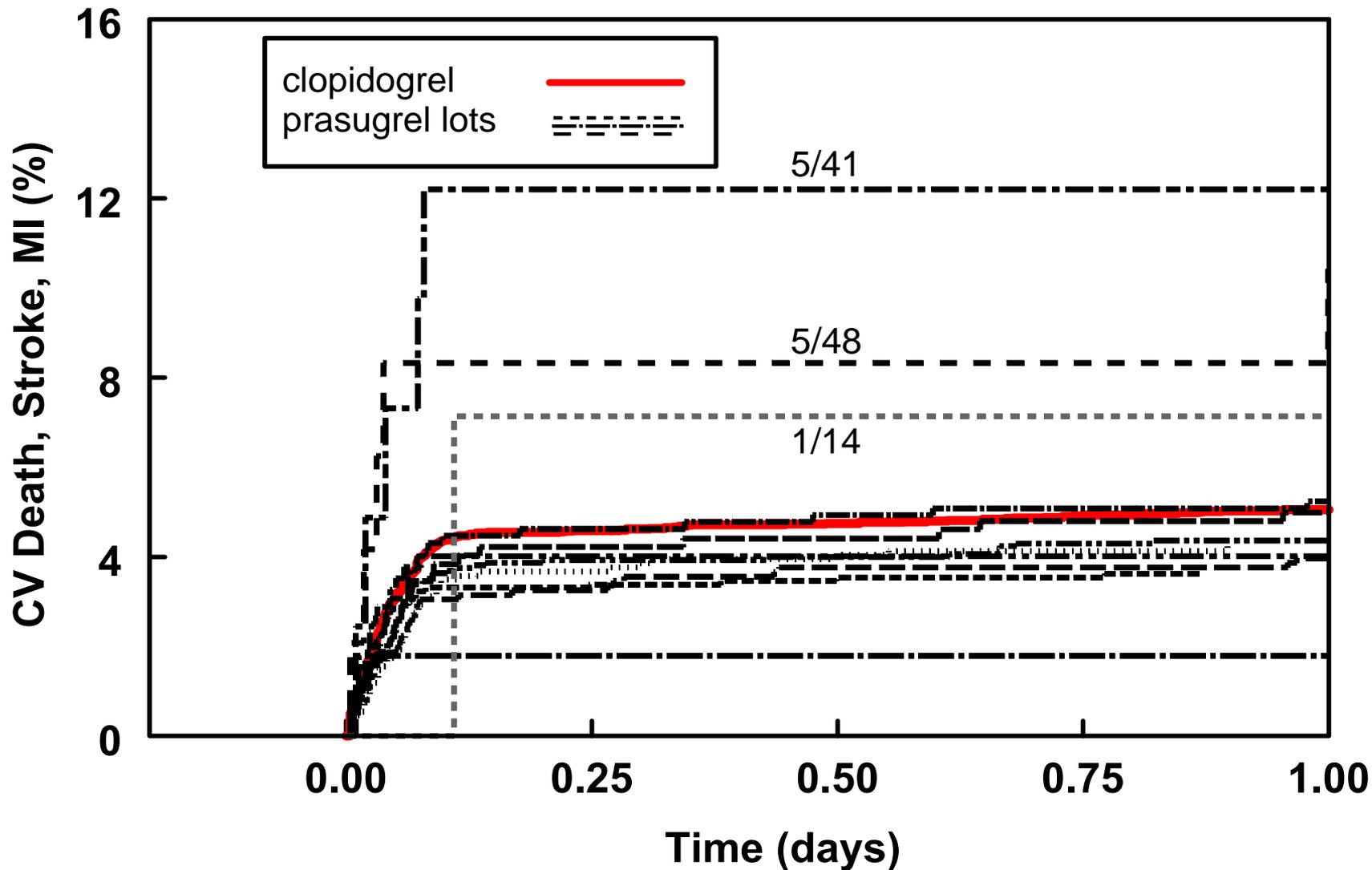


Pharmacodynamics: Prasugrel vs. Clopidogrel (Study TAAJ)

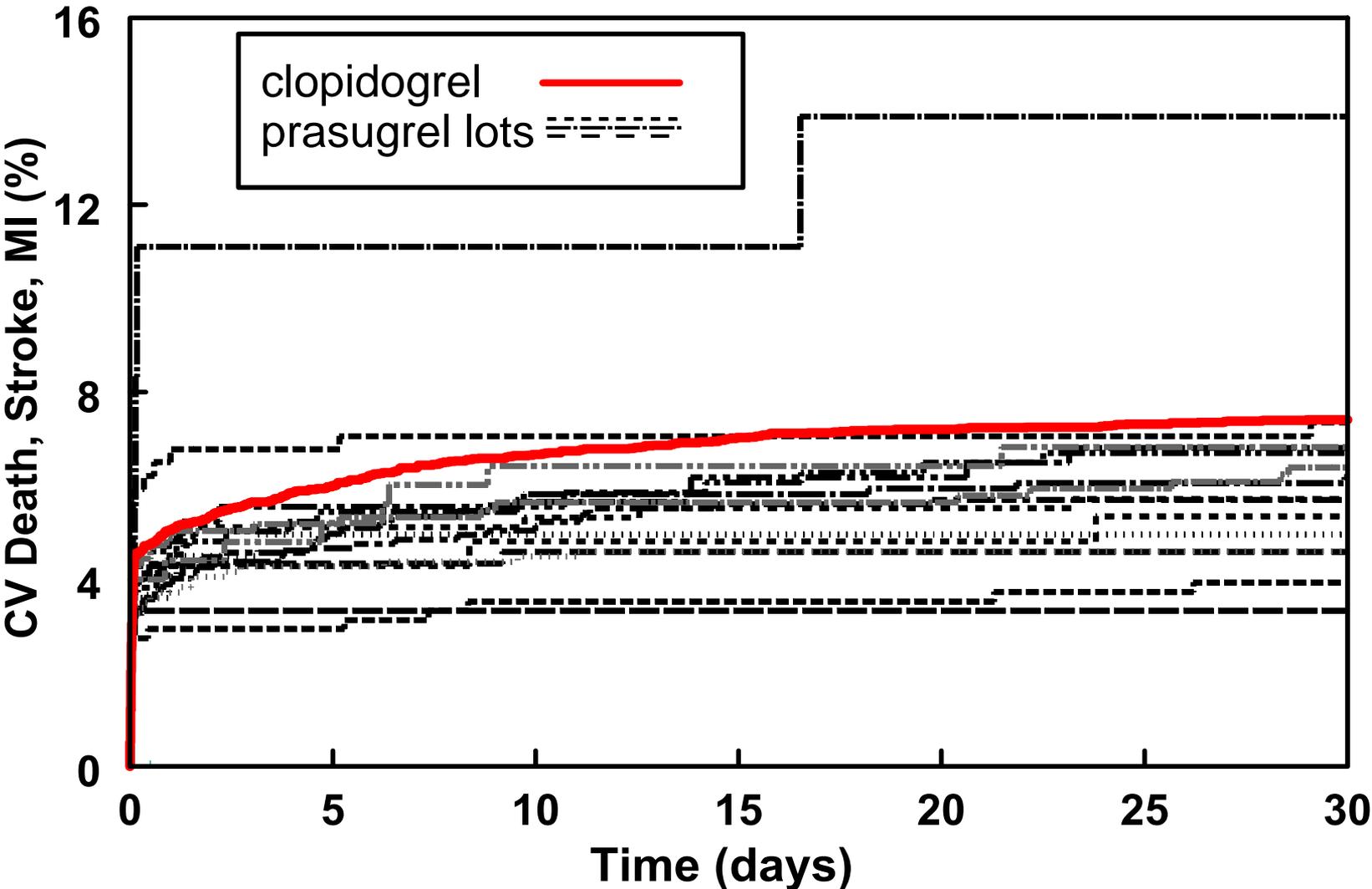


- **Inhibition of platelet aggregation (% IPA) following Prasugrel 60 mg or Clopidogrel 300 mg (mean \pm SD). Prasugrel's IPA exceeds that of clopidogrel at all time points.**

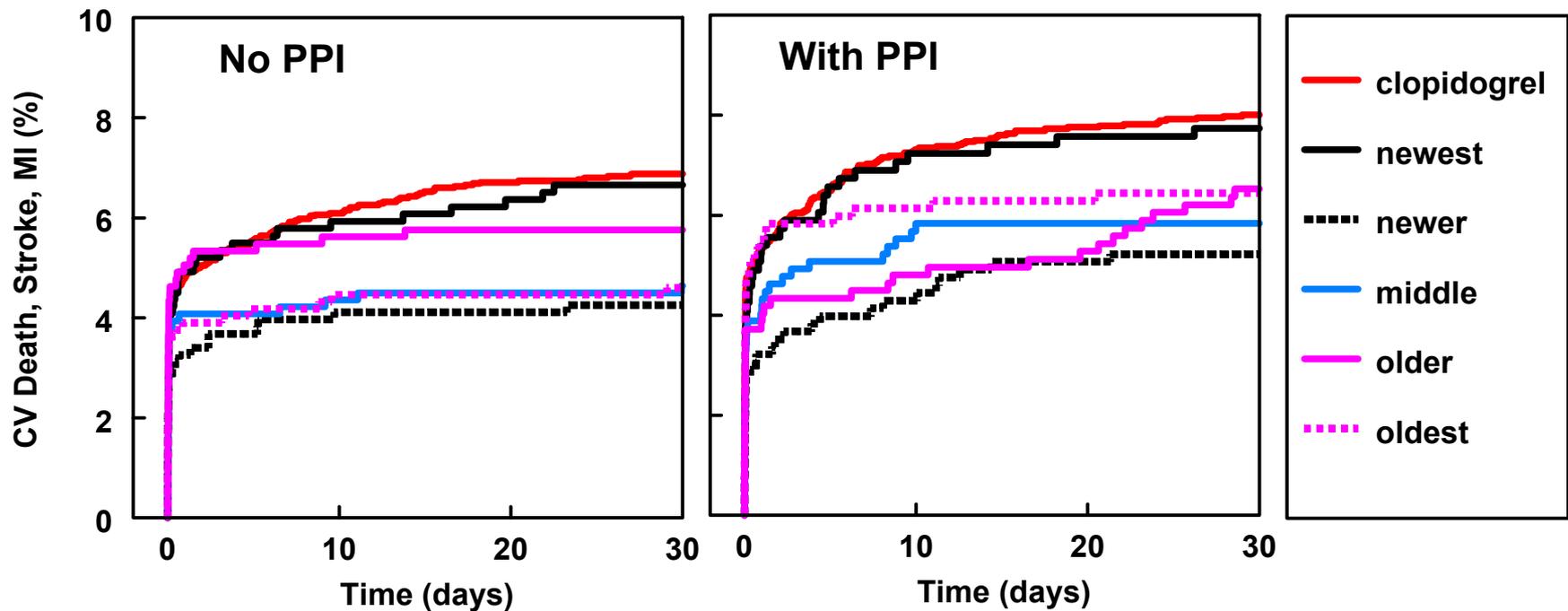
Primary Endpoint: Day 1 of Study, by Lot of Loading Dose



Primary Endpoint: Through Day 30, by Lot Days 2-30



Primary Endpoint: Age of Lot through Day 30



- No relationship between age of lot and efficacy, in presence or absence of PPI
- Hazard ratio = 0.82 with concomitant PPI use, 0.80 without

Salt to Base Conversion: Summary (1)

- **Bioequivalence in AUC for all levels of product conversion, 5% to 70%, with or without PPIs**
- **In absence of PPI, bioequivalence in C_{\max} for all levels of product conversion, 5% to 70%**
- **With concomitant PPI use, bioinequivalence in C_{\max} for all levels of product conversion**

Salt to Base Conversion: Summary (2)

Ramifications:

- Inequivalence in C_{\max} is tantamount to delay in reaching maximal effect, as determined by platelet aggregation.
- The delay in reaching maximal effect would affect loading dose, and could impact peri-procedural events.
- Delay would not affect daily maintenance therapy.

Salt to Base Conversion: Summary (3)

In the absence of PPI use:

- **Form conversion in the range 5% to 70% has no effect on bioavailability.**
- **Approximately 60% of subjects in TRITON were not using PPIs at any time. Thus, for non-PPI users, safety and efficacy are well-characterized.**

Salt to Base Conversion: Summary (4)

With concomitant PPI use:

- **Form conversion can only decrease bioavailability; it should not impact safety.**
- **The concern regarding decreased bioavailability is decreased efficacy.**
- **In TRITON, Prasugrel's efficacy was fairly consistent in all lots tested and across a spectrum of tablet ages, with and without PPI use.**

Salt to Base Conversion: Summary (5)

- Based on current manufacturing control strategy, to-be-marketed batches of Prasugrel tablets may contain significantly lower levels of base than batches used in TRITON.
- **For non-PPI users:** as long as form conversion of the to-be-marketed product is within the 5% to 70% range, it will be bioequivalent to the product tested in TRITON.
- **For PPI users:** a marketed product with less conversion than lots used in TRITON, but in the 5% to 70% range, would have enhanced bioavailability, but data from TRITON in non-PPI users supports its safety.

Prasugrel: Overall Benefit-Risk Profile

1000 patients treated with Prasugrel instead of Clopidogrel:

24 endpoint events prevented:

- 21 non-fatal myocardial infarctions
- 3 cardiovascular deaths
- 0 strokes

10 excess TIMI Major or Minor bleeding events:

- 2 bleeding deaths
- 3 non-fatal TIMI Major bleeds (ICH, or hemoglobin decrease ≥ 5 g/dL)
- 5 TIMI Minor bleeds (hemoglobin $\downarrow\downarrow \geq 3$ to < 5 g/dL)
 - and 19 TIMI Minimal bleeds.

- Cancer: causality uncertain, but potentially a continuing risk.

Questions?

Backup

Imbalance in Neoplasia: TRITON-TIMI 38

original classification

new classification

neoplasm location	prasugrel	clopidogrel
	n=6741	n=6716
brain	0	1
endocrine	1	0
oral cavity and pharynx	1	2
breast	3	1
lung and bronchus	16	12
other respiratory/thoracic	1	0
colorectal	19	10
esophagus	4	3
stomach	7	7
pancreas	2	3
liver	0	1
gallbladder/biliary	2	0
kidney	6	3
bladder	5	8
prostate	8	9
gynecologic	2	1
malignant melanoma	3	2
non-melanomatous skin	6	13
endocrine	1	0
leukemia	1	1
lymphoma	2	1
other hematologic	0	1
metastasis unknown primary	2	0
other unknown primary	0	1
unknown	2	0

all	94	80	RR = 1.18
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exclude non-melanomatous skin	88	67	RR = 1.31
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neoplasm location	prasugrel	clopidogrel
	n=6741	n=6716
brain	0	1
endocrine	1	0
oral cavity and pharynx	1	2
breast	3	1
lung and bronchus	16	12
other respiratory/thoracic	1	0
colorectal	19	9
esophagus	4	3
stomach	7	7
pancreas	2	3
liver	1	1
gallbladder/biliary	2	0
kidney	6	3
bladder	5	7
prostate	8	9
gynecologic	2	1
malignant melanoma	3	2
non-melanomatous skin	6	13
endocrine	1	0
leukemia	1	1
lymphoma	2	1
other hematologic	1	1
metastasis unknown primary	2	0
other unknown primary	0	1
unknown	2	0

all	96	78	RR = 1.23
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exclude non-melanomatous skin	90	65	RR = 1.38
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