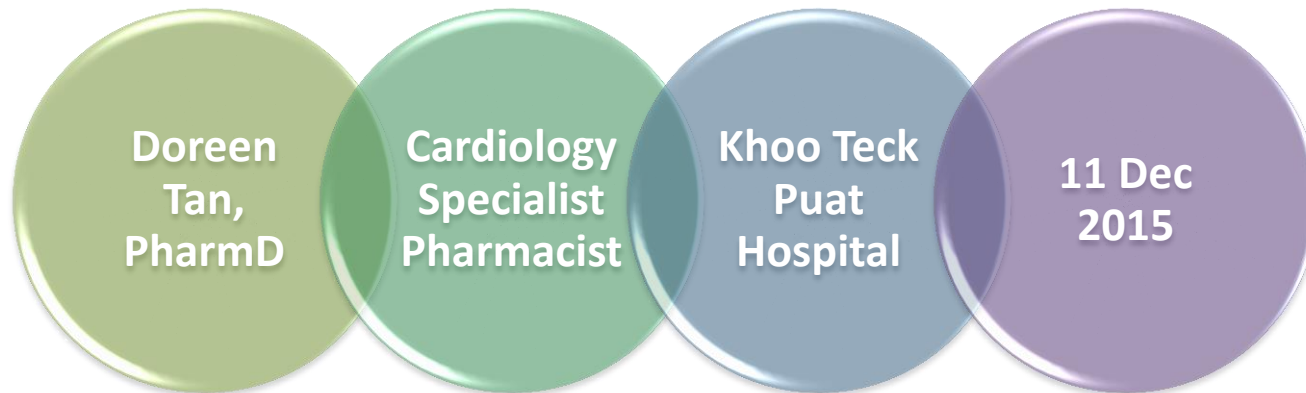


MegaDAPT Bleed

Single Center Registry Study
(Singapore)



Background

GI protectants recommended by several guidelines

Only 1 RCT: CREDO which studied effect of PPI with clopidogrel

- What about Ticagrelor & Prasugrel?

Do GI protectants really prevent GIB?

Bleeding outcomes (PLATO)

Advisory Committee Briefing Document
Drug Substance Ticagrelor
Date 23 June 2010

Table 21 Non-procedure-related 'Total Major' bleeding events by anatomic location - PLATO

| Primary location | Ticagrelor 90 mg bid N=9235 | Clopidogrel 75 mg qd N=9186 |
|---------------------|--------------------------------|--------------------------------|
| Total bleeds | 251 | 190 |
| Gastrointestinal | 124 | 94 |
| Intracranial | 27 | 14 |
| Urinary | 13 | 14 |
| Pericardial | 11 | 11 |
| Epistaxis | 11 | 8 |
| Subcutaneous/dermal | 11 | 4 |
| Hemoptysis | 6 | 3 |
| Retroperitoneal | 2 | 3 |
| Intraocular | 0 | 2 |
| Other | 46 | 37 |

Patients may be counted in >1 bleeding event category.

In the ticagrelor group, Patient E3907032 had 2 adjudicated 'Major Fatal/Life-threatening' intracranial bleeding events.

bid Twice daily dosing; qd Once daily dosing.

Sub-group analysis (PLATO)

Figure 1 Hazard ratios and rates of 'Total Major' (CABG included) bleeding events by selected patient subgroups – PLATO safety analysis set

| Characteristic | Hazard Ratio (95% CI) | Total Patients | Event Number T | Event Number C | HR (95% CI) |
|----------------|-----------------------|----------------|----------------|----------------|-------------------|
| Age Group | | | | | |
| < 65 years | | 10528 | 452 | 459 | 1.00 (0.87, 1.13) |
| > = 65 years | | 7892 | 509 | 470 | 1.07 (0.95, 1.22) |
| Age Group | | | | | |
| < 75 years | | 15574 | 793 | 756 | 1.04 (0.94, 1.15) |
| > = 75 years | | 2846 | 168 | 173 | 1.04 (0.84, 1.29) |
| Sex | | | | | |
| Male | | 13184 | 709 | 682 | 1.05 (0.94, 1.16) |
| Female | | 5237 | 252 | 247 | 1.01 (0.85, 1.21) |
| Race | | | | | |
| Caucasian | | 16899 | 881 | 850 | 1.04 (0.95, 1.14) |
| Black | | 222 | 12 | 15 | 0.74 (0.35, 1.59) |
| Asian | | 1081 | 53 | 52 | 1.03 (0.70, 1.51) |
| Other | | 219 | 15 | 12 | 1.30 (0.61, 2.78) |
| Weight | | | | | |
| < 60 kg | | 1296 | 72 | 87 | 0.82 (0.60, 1.12) |
| > = 60 kg | | 17086 | 887 | 839 | 1.06 (0.96, 1.16) |

Study Design: Retrospective, Cohort Study

Inclusion criteria

- All PCI patients with visits in 1 Aug 2013 – 31 Dec 2014 (17 mths)
- On Dual Antiplatelets

Exclusion criteria

- Non-cardiac PCI
- Missing data
- Duplicate visits
- Lost to follow-up
- Aspirin allergy

Outcomes

MACE and
bleeding

Index admission, followed
over 6 months

- Any visit to A&E, hospitalisation and/or procedures to manage bleeding

Endpoint Adjudication

Major Adverse Cardiovascular Endpoint

- Cutlip criteria (Circulation. 2007; 115:2344-2351)
 - Repeat revascularisation (TVR, TLR, ISR)
 - Stent Thrombosis
 - Myocardial Infarction
 - Death

Adjudication

2 Cardiologists + 2 Gastroenterologists

Bleeding

BARC criteria

- 1: Not actionable
- 2: Clinically overt signs of bleeding
- 3: Bleeding +
 - 3a: Transfusion + Hb drop 3-5 g/dL
 - 3b: Hb drop \geq bleed +5g/dL, require sx intervention, vasopressors
 - 3c: ICH, Intraocular bleeding affecting vision
- 4: CABG-related bleeding
- 5: Fatal bleeding
 - 5a: Probable
 - 5b: Definite

Recruitment statistics

**Cath Lab
patients**

(Aug 2013-Dec 2014)

After exclusion

N = 1013

Clopidogrel

N = 624

(61.6%)

Ticagrelor

N = 368

(36.3%)

Prasugrel

N = 21

(2.1%)

Baseline Demographics

| Characteristics | Overall n=1013 | Clopidogrel n= 624 | Ticagrelor n= 368 | Prasugrel n= 21 | p-value |
|-------------------------|-------------------|-----------------------|----------------------|--------------------|---------|
| Gender | | | | | |
| Male | 838 (82.7) | 498 (79.8) | 324 (88.0) | 16 (76.2) | 0.003 |
| Female | 175 (17.3) | 126 (20.2) | 44 (12.0) | 5 (23.8) | |
| Age | | | | | |
| Age (years), Mean (SD) | 56.7 (±10.4) | 57.2 (±10.8) | 56.0 (±9.7) | 56.1 (±9.0) | 0.626 |
| Age <60 Years Old | 651 (64.3) | 387 (62.0) | 249 (67.7) | 15 (71.4) | 0.158 |
| Age ≥60 Years Old | 362 (35.7) | 237 (38.0) | 119 (32.3) | 6 (28.6) | |
| Age <75 Years Old | 952 (94.0) | 578 (92.6) | 353 (95.9) | 21(100) | 0.055 |
| Age ≥75 Years Old | 61 (6.0) | 46 (7.4) | 15 (4.1) | 0 (0.0) | |
| Weight (kg) | | | | | |
| ≥60kg | 787 (77.7) | 484 (77.6) | 286 (77.7) | 17 (81.0) | 0.583 |
| <60kg | 176 (17.4) | 114 (18.3) | 59 (16.0) | 3 (14.3) | |
| Data Missing | 50 (4.9) | 26 (4.2) | 23 (6.3) | 1 (4.8) | |
| Ethnicity | | | | | |
| Chinese | 500 (49.4) | 302 (48.4) | 188 (51.5) | 10 (47.6) | 0.786 |
| If Malay | 240 (23.7) | 153 (24.5) | 81 (22.0) | 6 (28.6) | |
| If Indians | 203 (20.0) | 122 (19.6) | 78 (21.2) | 3 (14.3) | |
| If Eurasians and Others | 70 (6.9) | 47 (7.5) | 21 (5.7) | 2 (9.5) | |

Baseline Demographics (2)

| Characteristics | Overall n=1013 | Clopidogrel n= 624 | Ticagrelor n= 368 | Prasugrel n= 21 | p-value |
|--------------------------|-------------------|-----------------------|----------------------|--------------------|---------|
| Comorbidities | | | | | |
| Hypertension | 570 (56.3) | 375 (60.1) | 180 (48.9) | 15 (71.4) | 0.001 |
| Hyperlipidaemia | 619 (61.1) | 415 (66.5) | 188 (51.1) | 16 (76.2) | <0.001 |
| Type 2 Diabetes Mellitus | 399 (39.4) | 274 (43.9) | 110 (29.9) | 15 (71.4) | <0.001 |
| Stroke/TIA | 48 (4.7) | 34 (5.4) | 13 (3.5) | 1 (4.8) | 0.390 |
| Chronic Kidney Disease | 53 (5.2) | 45 (7.2) | 6 (1.6) | 2 (9.5) | <0.001 |
| Cancer | 12 (1.2) | 9 (1.4) | 3 (0.8) | 0 (0.0) | 0.596 |
| History of Bleeding | 40 (3.9) | 27 (4.3) | 12 (3.3) | 1 (0.1) | 0.694 |
| Platelet Count | | | | | |
| Normal | 982 (96.9) | 598 (95.8) | 363 (98.6) | 21 (100) | 0.033 |
| Abnormal | 31 (3.1) | 26 (4.2) | 5 (1.4) | 0 (0.0) | |
| Smoking Status | | | | | |
| Non-Smokers | 500 (49.4) | 322 (51.6) | 165 (44.8) | 13 (61.9) | 0.011 |
| Current Smokers | 436 (43.0) | 247 (39.6) | 183 (49.7) | 6 (28.6) | |
| Missing Data | 77 (7.6) | 55 (8.8) | 20 (5.4) | 2 (9.5) | |

Baseline Demographics (3)

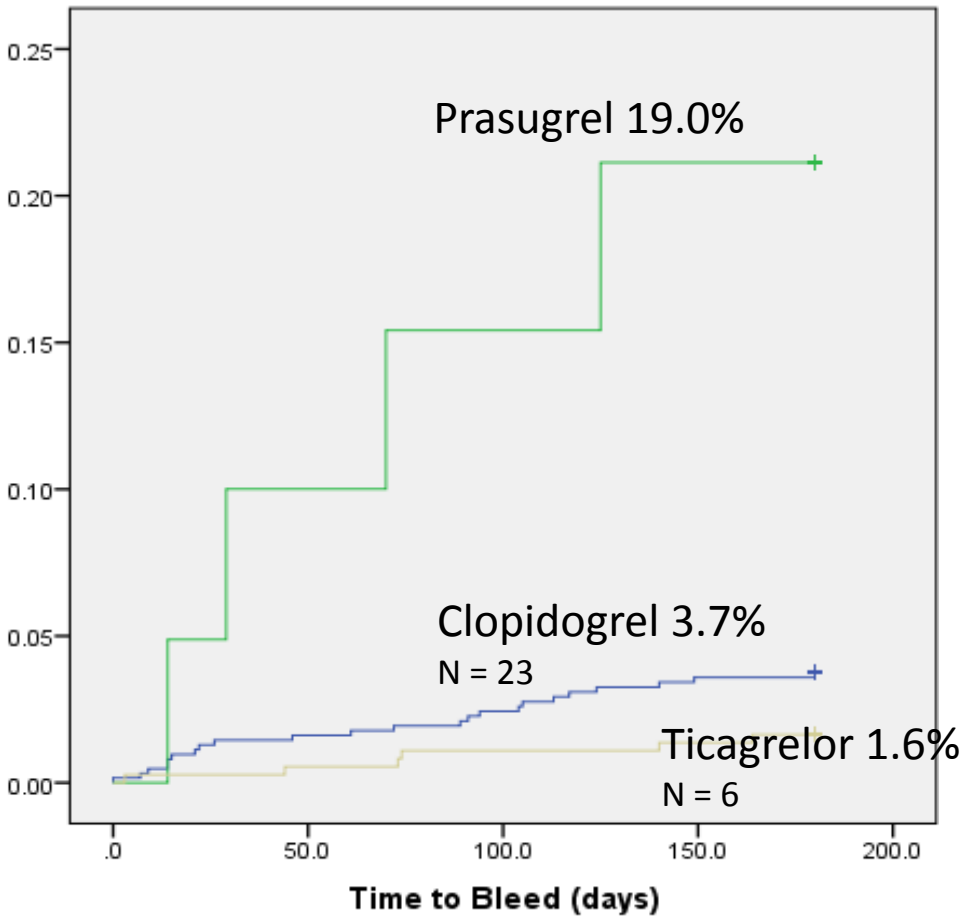
| Characteristics | Overall n=1013 | Clopidogrel n= 624 | Ticagrelor n= 368 | Prasugrel n= 21 | p-value |
|------------------------------|-------------------|-----------------------|----------------------|--------------------|---------|
| Ejection Fraction | | | | | |
| >40% | 711 (70.2) | 447 (71.6) | 247 (67.1) | 17 (81.0) | 0.086 |
| ≤40% | 226 (22.3) | 126 (20.2) | 98 (26.6) | 2 (9.5) | |
| Data Missing | 76 (7.5) | 51 (8.2) | 23 (6.3) | 2 (9.5) | |
| Staged PCI | | | | | |
| No | 981 (96.8) | 596 (95.5) | 366 (99.5) | 19 (90.5) | 0.001 |
| Yes | 32 (3.2) | 28 (24.5) | 2 (0.5) | 2 (9.5) | |
| ACS : PCI Indications | | | | | |
| Unstable Angina | 91 (9.0) | 76 (12.2) | 13 (3.5) | 2 (9.5) | <0.001 |
| STEMI | 434 (42.8) | 134 (21.5) | 297 (80.7) | 3 (14.3) | |
| NSTEMI | 309 (30.5) | 267 (42.8) | 34 (9.2) | 8 (38.1) | |
| Evolved MI | 17 (1.7) | 13 (2.1) | 3 (0.8) | 1 (4.8) | |
| Others | 162 (16.0) | 134 (21.5) | 21 (5.7) | 7 (33.3) | |
| No. of Stents | | | | | |
| 0 (Ref) | 59 (5.8) | 46 (7.4) | 12 (3.3) | 1 (4.8) | 0.157 |
| 1 | 682 (67.3) | 422 (67.6) | 249 (67.7) | 11 (52.4) | |
| 2 | 220 (21.7) | 127 (20.4) | 85 (23.1) | 8 (38.1) | |
| 3 | 45 (4.4) | 25 (4.0) | 19 (5.2) | 1 (4.8) | |
| 4 | 7 (0.7) | 4 (0.6) | 3 (0.8) | 0 (0.0) | |
| Type of Stents | | | | | |
| Bare Metal Stents | 407 (40.2) | 231 (37.0) | 168 (45.7) | 8 (38.1) | 0.075 |
| Drug Eluting Stents | 501 (49.5) | 320 (51.3) | 171 (46.5) | 10 (47.6) | |
| Both | 31 (3.1) | 17 (2.7) | 12 (3.3) | 2 (9.5) | |
| POBA and DEB | 60 (5.9) | 47 (7.5) | 12 (3.3) | 1 (4.8) | |
| Bioabsorbable | 8 (0.8) | 6 (1.0) | 2 (0.5) | 0 (0.0) | |
| Bioactive | 6 (0.6) | 3 (0.5) | 3 (0.8) | 0 (0.0) | |

Baseline Demographics (GI protectant use)

| Characteristics | Overall n=1013 | Clopidogrel n= 624 | Ticagrelor n= 368 | Prasugrel n= 21 | p-value |
|--------------------------|-------------------|-----------------------|----------------------|--------------------|---------|
| GI Protectants | | | | | |
| No PPI No H2RA (ref) | 464 (45.8) | 297 (47.6) | 156 (42.4) | 11 (52.4) | <0.001 |
| PPI only | 325 (32.1) | 159 (25.5) | 160 (43.5) | 6 (28.6) | |
| H2RA only | 197 (19.4) | 154 (24.7) | 39 (10.6) | 4 (19.0) | |
| Both PPI and H2RA | 27 (2.7) | 14 (2.2) | 13 (3.5) | 0 (0.0) | |
| PPI | | | | | |
| No PPI (Ref) | 651 (64.3) | 451 (72.5) | 195 (53.0) | 15 (71.4) | <0.001 |
| Low Dose (<40mg/day) | 154 (15.2) | 77 (12.3) | 72 (19.6) | 3 (14.3) | |
| High Dose (≥40mg/day) | 208 (20.5) | 96 (15.4) | 101 (27.4) | 3 (14.3) | |
| H2RA | | | | | |
| No H2RA (Ref) | 788 (77.8) | 455 (72.9) | 316 (85.9) | 17 (81.0) | <0.001 |
| Low Dose (<40mg/day) | 94 (9.3) | 72 (11.5) | 20 (5.4) | 2 (9.5) | |
| High Dose (≥40mg/day) | 131 (12.9) | 97 (15.5) | 32 (8.7) | 2 (9.5) | |

Bleeding

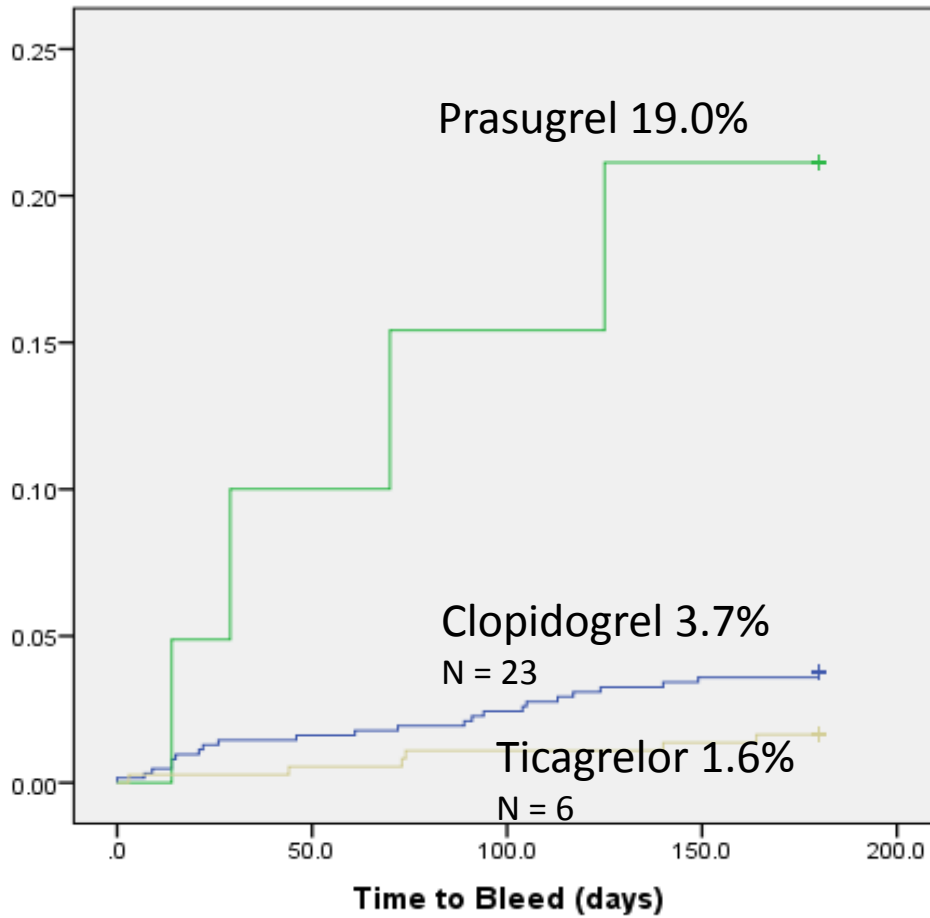
- $P < 0.001$



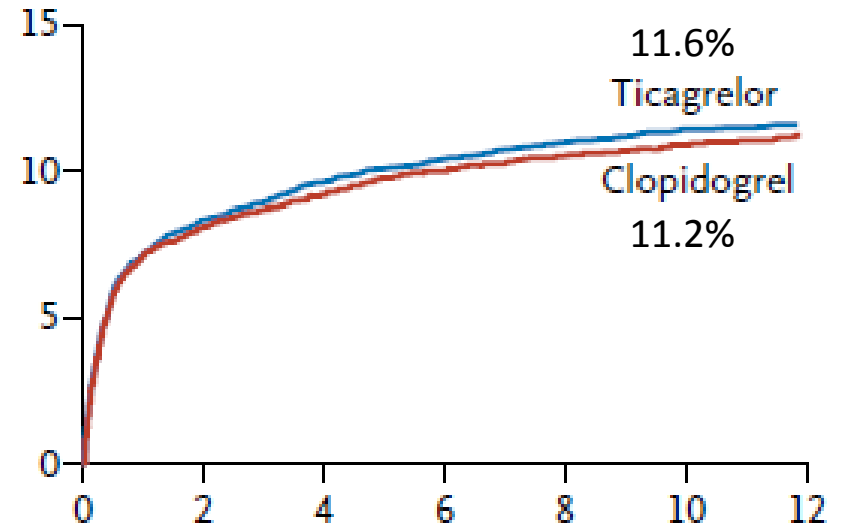
| Characteristics | Overall n=1013 | Clopidogrel n= 624 | Ticagrelor n= 368 | Prasugrel n= 21 |
|-----------------------|-------------------|-----------------------|----------------------|--------------------|
| No Bleeds | 980 (96.7) | 601 (96.3) | 362 (98.4) | 17 (81.0) |
| Type 1 | 4 (0.4) | 3 (0.5) | 1 (0.3) | 0 (0.0) |
| Type 2 | 11 (1.1) | 9 (1.4) | 1 (0.3) | 1 (4.8) |
| Type 3a | 5 (0.5) | 5 (0.8) | 0 (0.0) | 0 (0.0) |
| Type 3b | 10 (1.0) | 4 (0.6) | 3 (0.8) | 3 (14.3) |
| Type 3c | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Type 4: CABG | 1 (0.1) | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| Type 5a | 1 (0.1) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Type 5b | 1 (0.1) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Total Bleeding | 33 (3.3) | 23 (3.7) | 6 (1.6) | 4 (19.0) |

Bleeding

MegaDAPT



PLATO



Predictors for bleeding

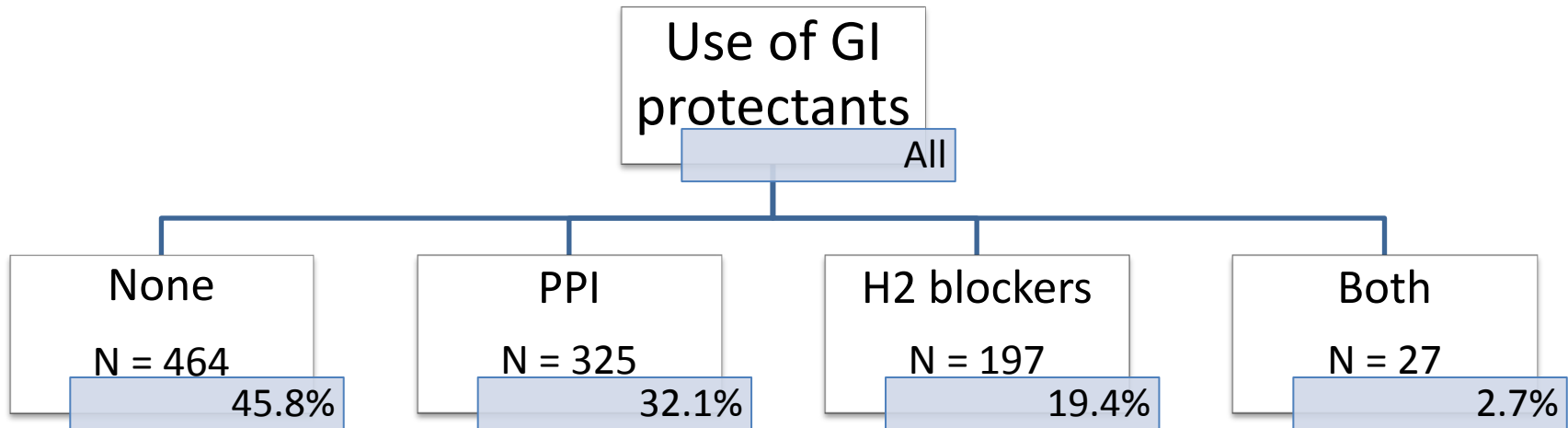
| Factor | OR | CI | Sig |
|------------------------------|-------|----------------|-------|
| Indian compared with Chinese | 0.031 | 0.057-0.869 | 0.031 |
| Ticagrelor vs Clopidogrel | 0.381 | 0.143-1.015 | 0.054 |
| Hypertension | 3.854 | 1.210 – 12.278 | 0.022 |
| Anticoagulation | 5.030 | 1.145 – 22.102 | 0.032 |
| Prasugrel vs Clopidogrel | 9.152 | 2.397-34.940 | 0.001 |
| CYP3A4 inhibitor vs none | 9.910 | 2.529-38.829 | 0.001 |

Controlled for age, gender, smoking, hyperlipidemia, DM, CKD, GI protectants, EF

Location of bleeding

| | N | % |
|----------------------------|----|-------|
| Gastro-Intestinal Bleeding | 22 | 66.7 |
| ENT | 2 | 6.1 |
| Central Nervous System | 2 | 6.1 |
| Genitourinary | 2 | 6.1 |
| Others | 5 | 15.1 |
| Total | 33 | 100.0 |

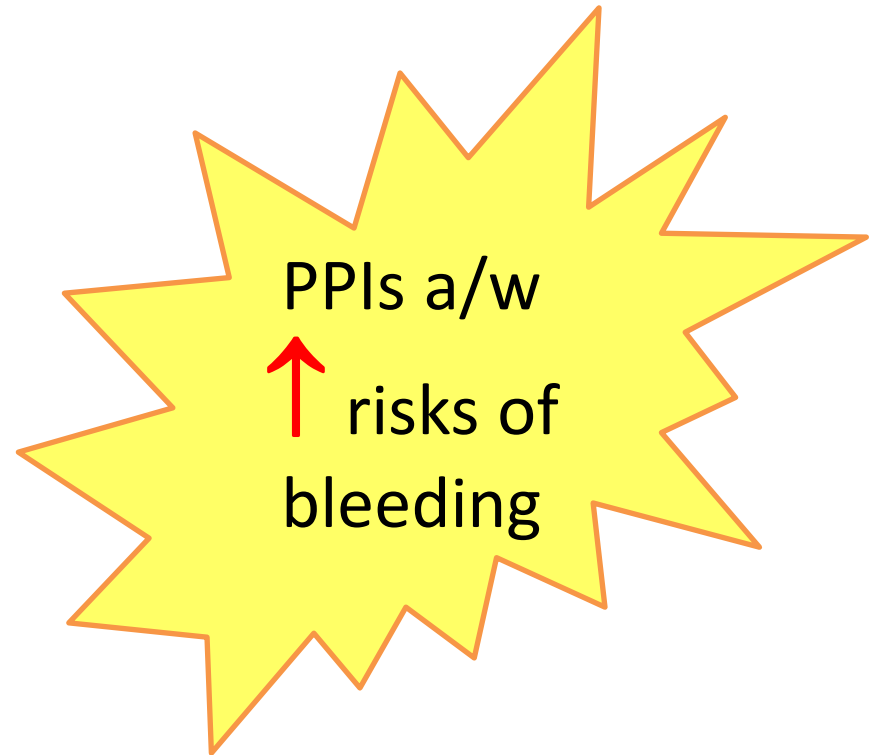
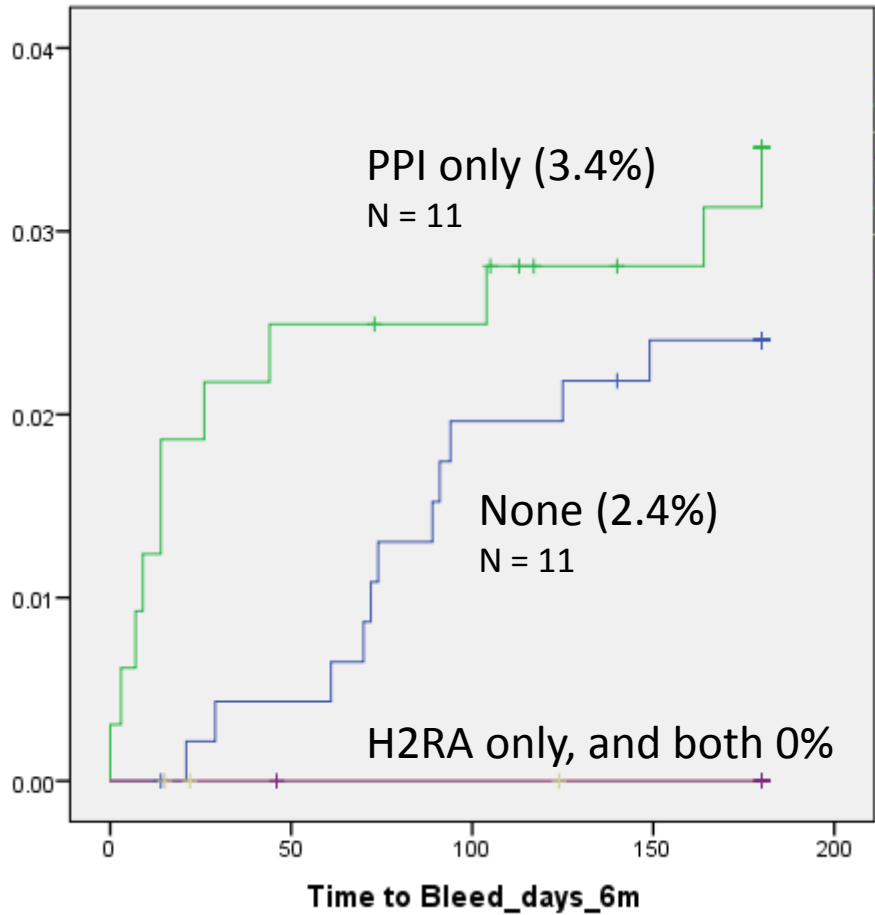
Use of GI protectants



| | Clopidogrel n= 624 | Ticagrelor n= 368 | Prasugrel n= 21 |
|--------------------------|-------------------------------|------------------------------|----------------------------|
| None | 297 (47.6) | 156 (42.4) | 11 (52.4) |
| PPI only | 159 (25.5) | 160 (43.5) | 6 (28.6) |
| H2RA only | 154 (24.7) | 39 (10.6) | 4 (19.0) |
| Both PPI and H2RA | 14 (2.2) | 13 (3.5) | 0 (0.0) |

P < 0.001

GI bleeding



Predictors for GI bleeding

| Factor | OR | CI | Sig |
|--------------------------|-------|-------------|--------|
| EF≤40% | 2.96 | 0.99-8.81 | 0.051 |
| Anticoagulation | 11.74 | 2.36-58.43 | 0.003 |
| CYP3A4 inhibitor vs none | 12.23 | 2.67-56.16 | 0.001 |
| Prasugrel | 23.90 | 5.54-103.22 | <0.001 |
| COXII vs none | 23.57 | 1.98-281.33 | 0.012 |

Though the use of high dose PPI associated with more GIB with univariate analysis, PPI use did not modify risk of bleeding

Conclusion

Avoid Prasugrel if concern is that of bleeding

Approx 2/3 of bleeds are GIB, not modified by PPI use

- Should PPIs be used routinely for DAPT patients?

Other GIB risk factors are important:

- Anticoagulation, COXII, use of CYP3A4 inhibitors

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THANK YOU!