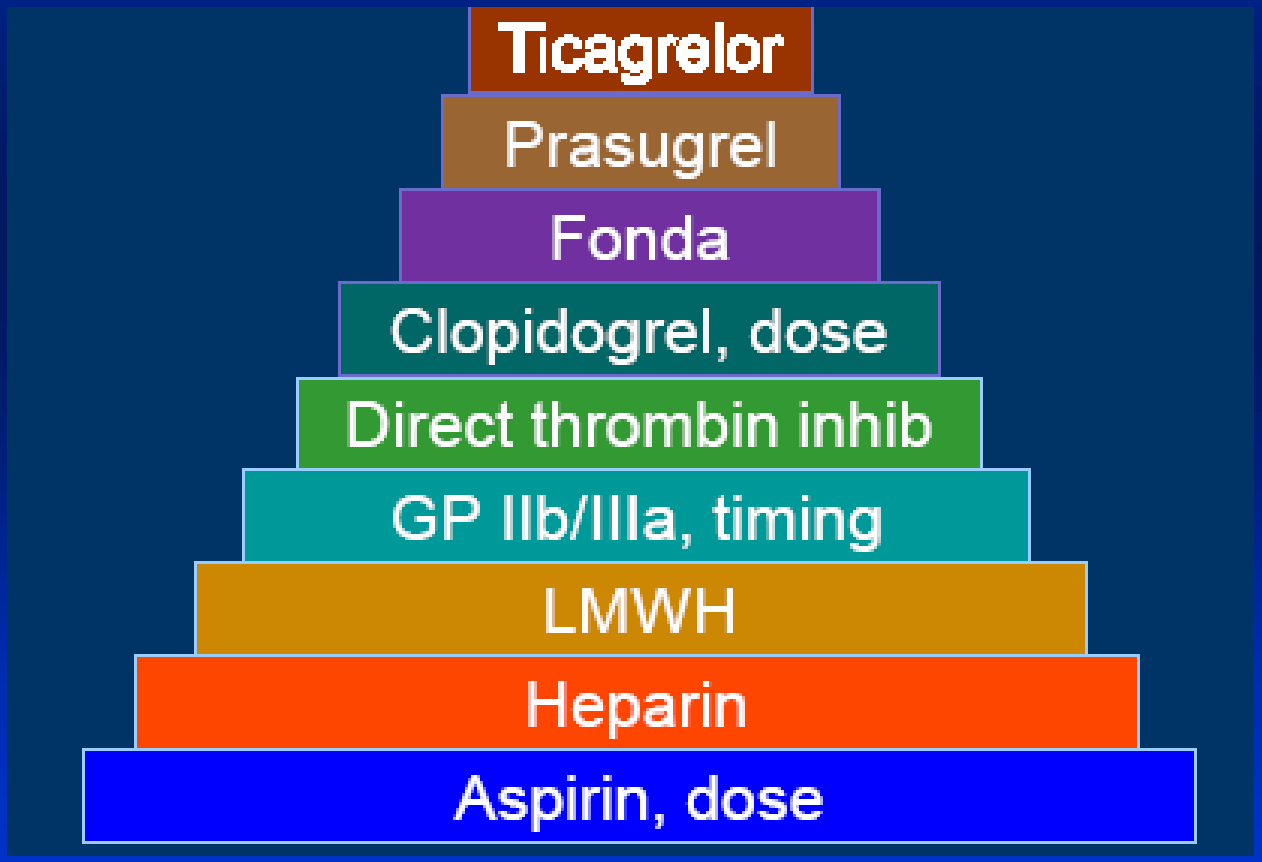
Non-ST Elevation Acute Coronary Syndrome – Tailoring Antiplatelet Therapy in Different Subgroups

David Hasdai, MD

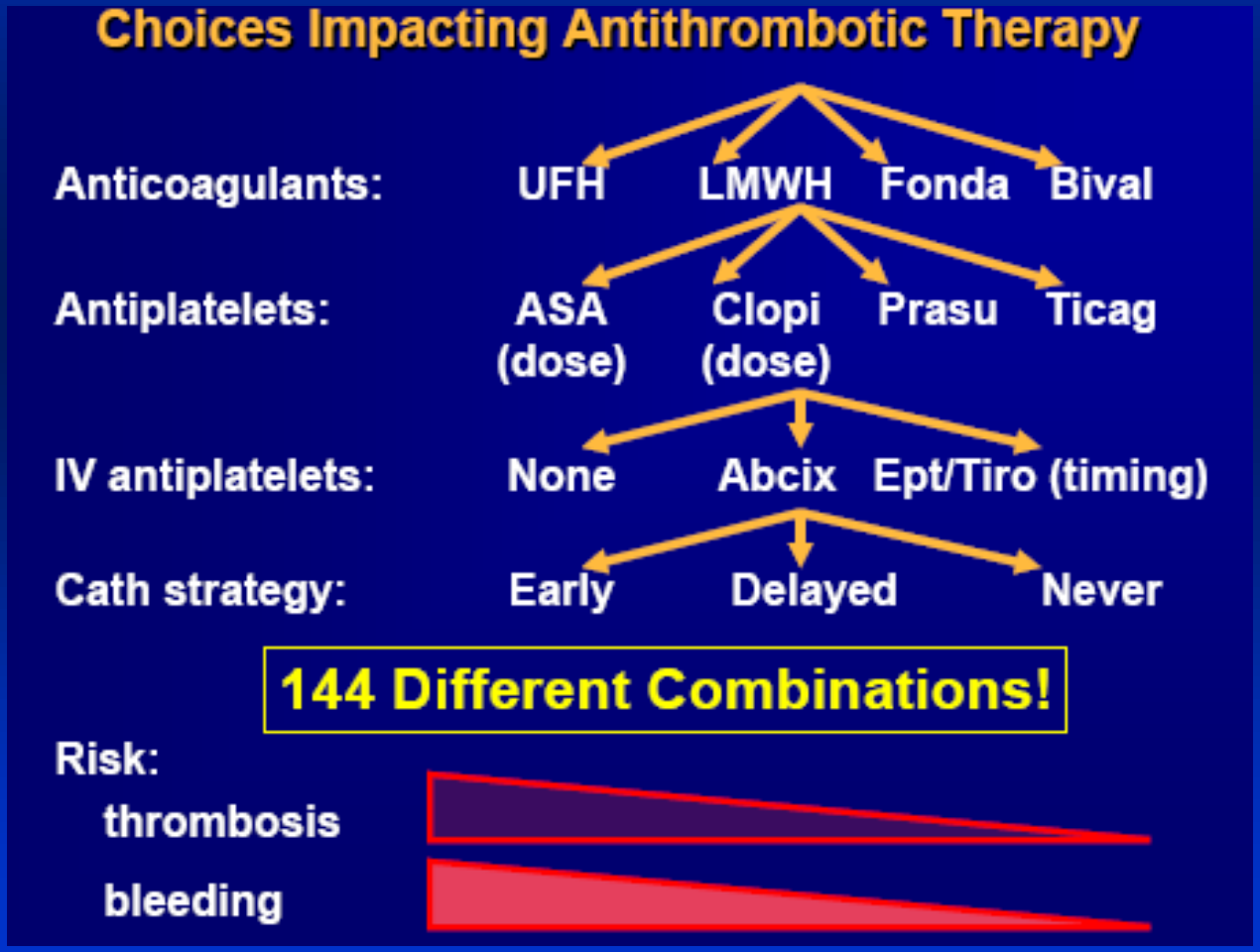
Professor, Tel Aviv University, Israel

Rabin Medical Center, Petah Tikva, Israel

Tower of Babel



Different Strokes for Different Folks – *The Strokes*



Different Strokes for Different Folks – *The Folks*

- **Age**
- **Weight**
- **Prior CVA/TIA**
- **Diabetes Mellitus**
- **GRACE/TIMI score**
- **CRUSADE bleeding score**
- **Invasive vs Conservative Mgt**
- **Timing of Invasive Mgt**
- **Likelihood of CABG/surgery**
- **Concomitant anticoagulant Rx**
- **Rx compliance**

European Heart Journal
doi:10.1093/eurheartj/ehr236

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Christian W. Hamm (Chairperson) (Germany)*, Jean-Pierre Bassand (Co-Chairperson)*, (France), Stefan Agewall (Norway), Jeroen Bax (The Netherlands), Eric Boersma (The Netherlands), Hector Bueno (Spain), Pio Caso (Italy), Dariusz Dudek (Poland), Stephan Gielen (Germany), Kurt Huber (Austria), Magnus Ohman (USA), Mark C. Petrie (UK), Frank Sonntag (Germany), Miguel Sousa Uva (Portugal), Robert F. Storey (UK), William Wijns (Belgium), Doron Zahger (Israel).

**ESC Committee for Practice Guidelines: Jeroen J. Bax (Chairperson) (The Netherlands), Angelo Auricchio (Switzerland), Helmut Baumgartner (Germany), Claudio Ceconi (Italy), Veronica Dean (France), Christi Deaton (UK), Robert Fagard (Belgium), Christian Funck-Brentano (France), David Hasdai (Israel), Arno Hoes (The Netherlands), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Theresa McDonagh (UK), Cyril Moulin (France), Don Poldermans (The Netherlands), Bogdan A. Popescu (Romania), Željko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Adam Torbicki (Poland), Alec Vahanian (France), Stephan Windecker (Switzerland).

European Heart Journal
Advance Access published August 26, 2011

$P2Y_{12}$ inhibitor recommendations 1

A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding

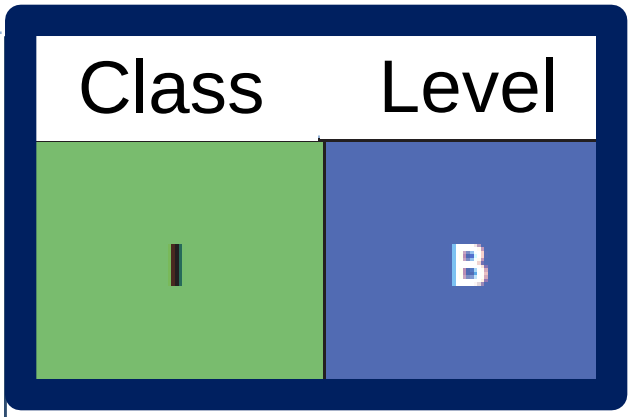
Class	Level
I	A

A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (H. pylori infection, age ≥65 years, concurrent use of anticoagulants or steroids)

Class	Level
I	A

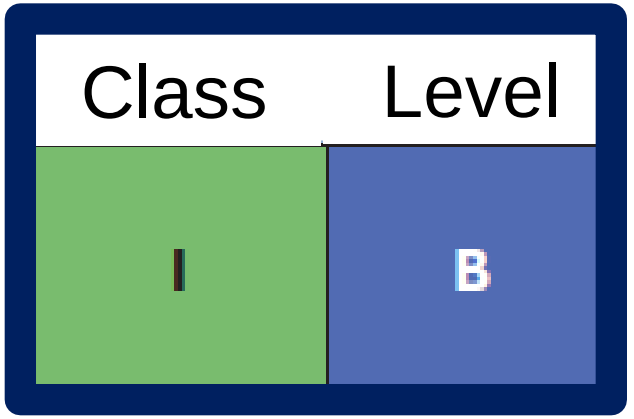
Ticagrelor

Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced)



Prasugrel

Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of lifethreatening bleeding or other contraindications



Clopidogrel dosing

Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel

Class	Level
I	A

A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option

Class	Level
I	B

A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding

Class	Level
IIa	B

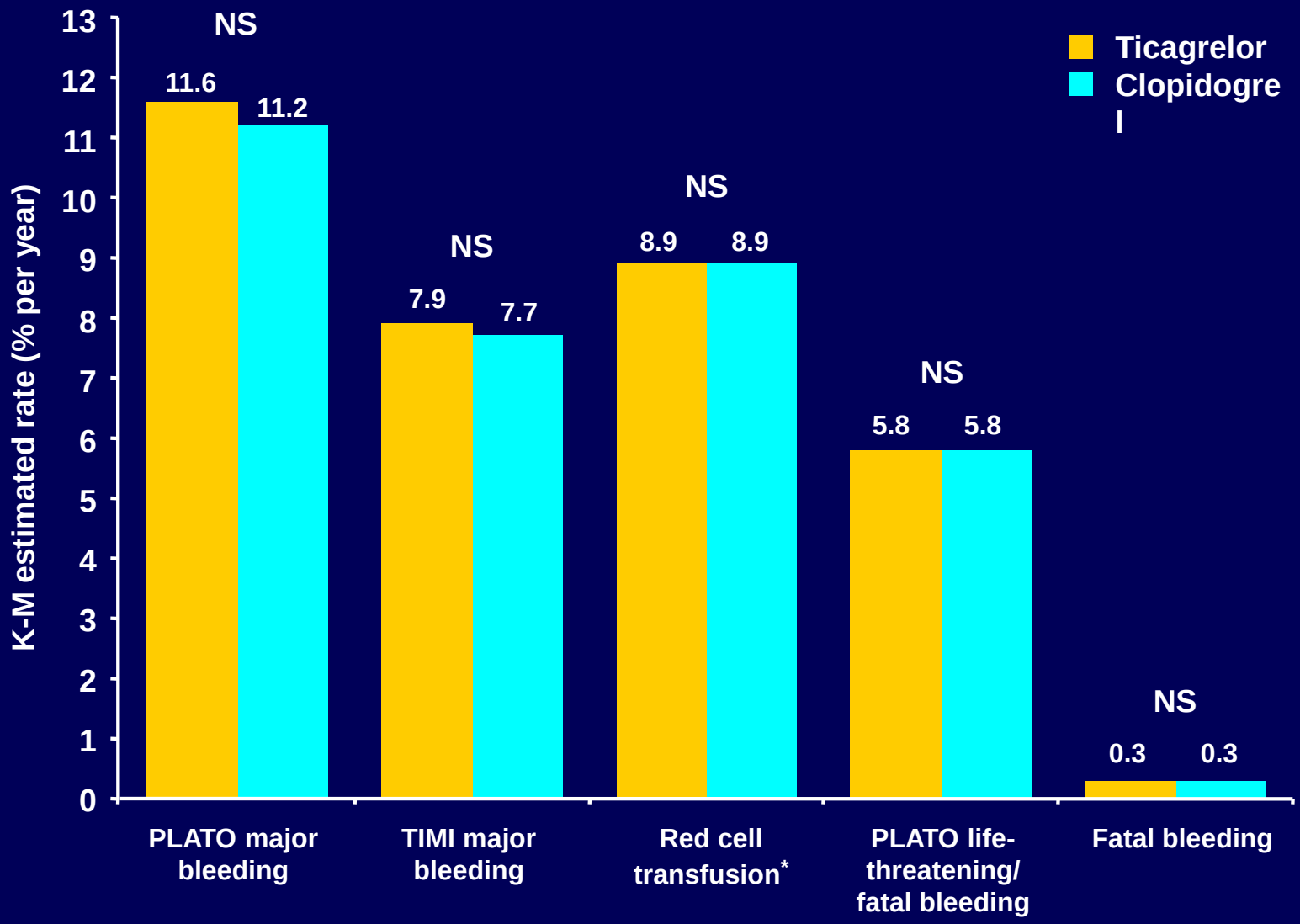
Different Strokes for Different Folks – *The Folks On Ticagrelor*

- **Age - Not an Issue**
- **Weight – Not an Issue**
- **Prior CVA/TIA – Not an Issue**
- **Diabetes Mellitus**
- **GRACE/TIMI score**
- **CRUSADE bleeding score**
- **Invasive vs Conservative Mgt**
- **Timing of Invasive Mgt**
- **Likelihood of CABG/surgery**
- **Concomitant anticoagulant Rx**
- **Rx compliance**

Different Strokes for Different Folks – *The Folks On Ticagrelor*

- **Age - Not an Issue**
- **Weight – Not an Issue**
- **Prior CVA/TIA – Not an Issue**
- **Diabetes Mellitus**
- **GRACE/TIMI score**
- **CRUSADE bleeding score - ???!!!**
- **Invasive vs Conservative Mgt**
- **Timing of Invasive Mgt**
- **Likelihood of CABG/surgery - ???!!!**
- **Concomitant anticoagulant Rx**
- **Rx compliance**

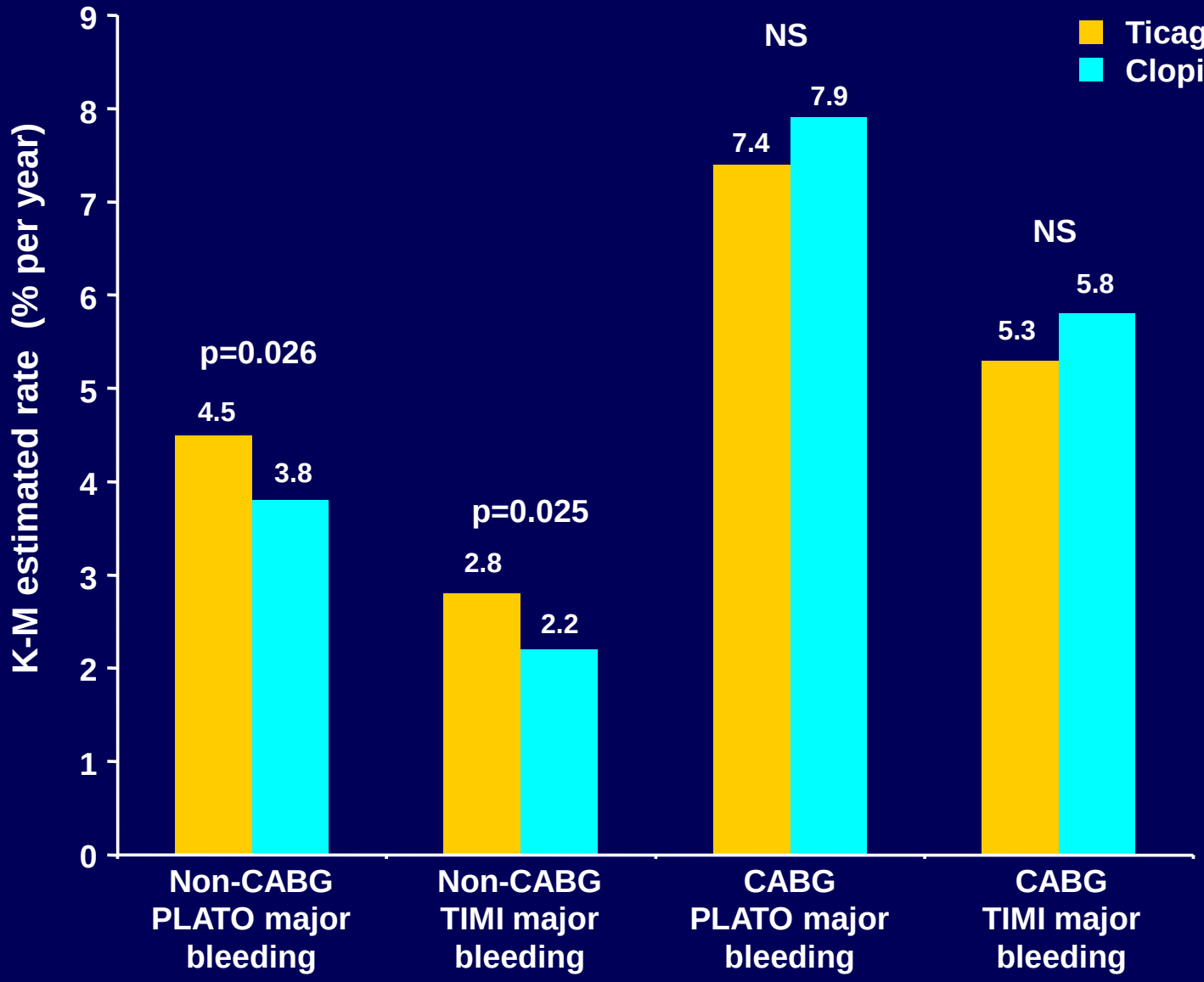
Total major bleeding



Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. NEJM 2007;357:2001–15;
*Proportion of patients (%); NS = not significant

Non-CABG and CABG-related major bleeding

PLATO



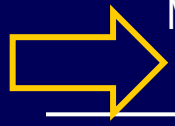
$P2Y_{12}$ Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect[a]	2–4 h	30 min	30 min
Duration of effect	3–10 days	5–10 days	3–4 days
Withdrawal before major surgery	5 days	7 days	5 days

Procedures and timing*

PLATO Invasive

Procedure	Ticagrelor (n=6,732)	Clopidogrel (n=6,676)
Invasive procedures at index hospitalization, % (n)		
Coronary angiography	**96.8 (6514)**	**96.9 (6471)**
Median (IQR), hours	**0.62 (0.10, 3.70)**	**0.62 (0.12, 3.65)**
PCI during index hospitalization % (n)	**76.7 (5166)**	**77.1 (5148)**
Median (IQR), hours	**0.77 (0.30, 2.75)**	**0.78 (0.32, 2.65)**
UA/NSTEMI – PCI % (n)	**63.8 (1882)**	**64.8 (1854)**
Median (IQR), hours	**2.63 (0.78, 21.10)**	**2.60 (0.87, 21.30)**
STEMI - Primary PCI % (n)	**83.2 (3138)**	**82.7 (3149)**
Median (IQR), hours	**0.47 (0.23, 0.95)**	**0.48 (0.23, 0.95)**
Coronary by-pass surgery pre-discharge % (n)	**5.5 (372)**	**6.1 (410)**
Median (IQR), hours	**117 (47, 216)**	**121 (48, 218)**

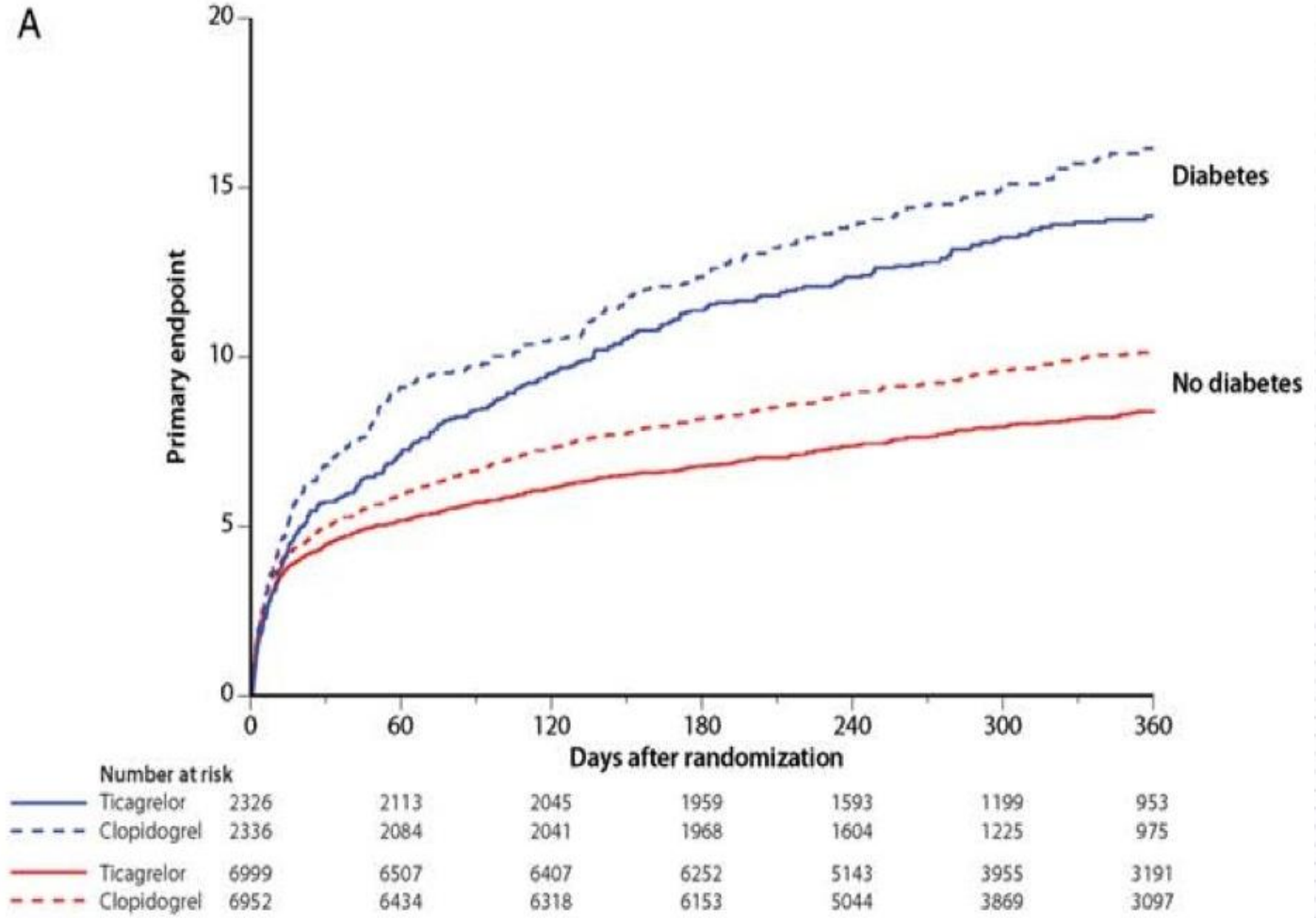


* Time between randomization and first procedure

Different Strokes for Different Folks – *The Folks On Ticagrelor*

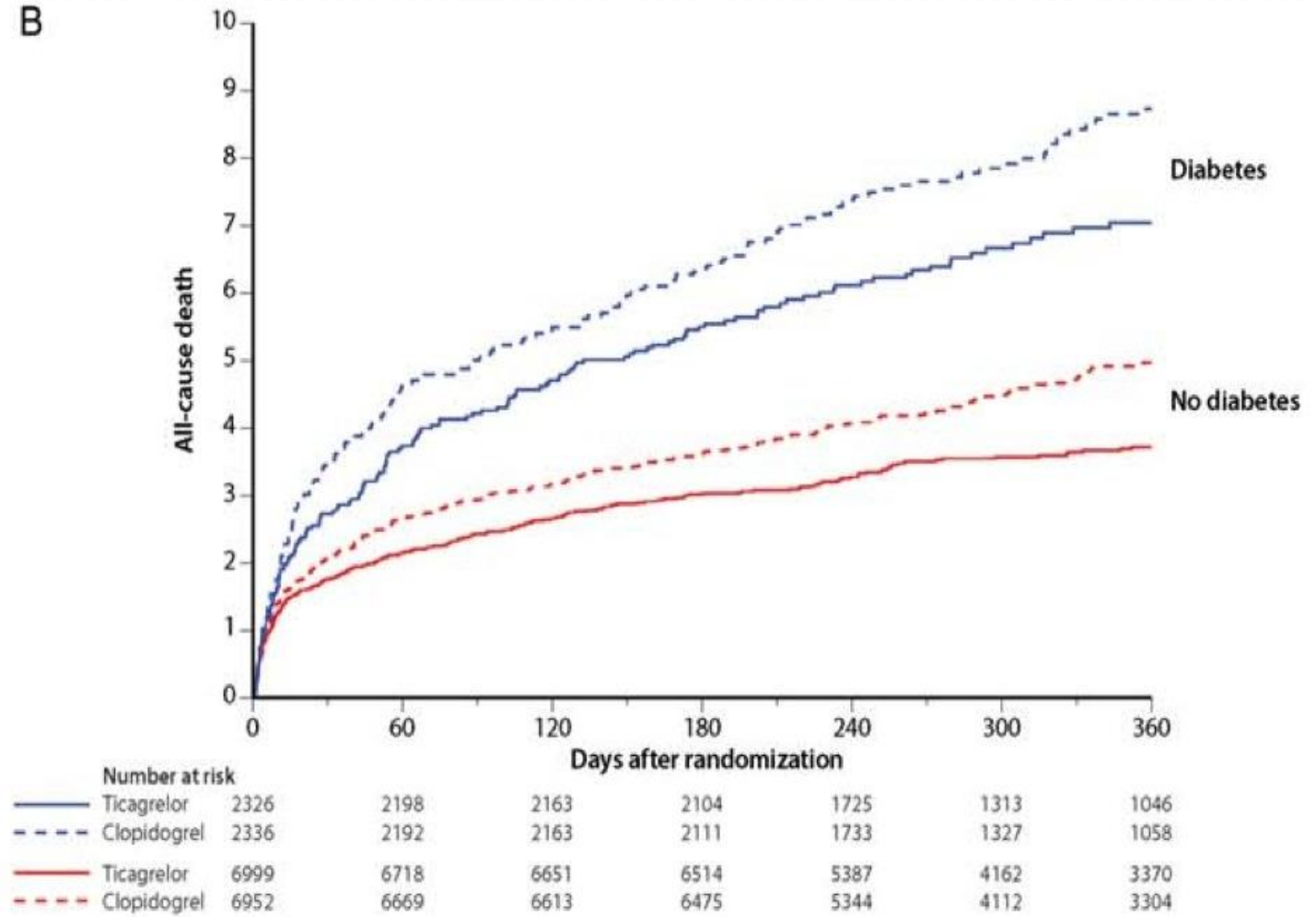
- **Age - Not an Issue**
- **Weight – Not an Issue**
- **Prior CVA/TIA – Not an Issue**
- **Diabetes Mellitus**
- **GRACE/TIMI score**
- **CRUSADE bleeding score**
- **Invasive vs Conservative Mgt**
- **Timing of Invasive Mgt**
- **Likelihood of CABG/surgery**
- **Concomitant anticoagulant Rx**
- **Rx compliance**

PLATO (ticagrelor vs. clopidogrel)
Diabetes substudy primary end point



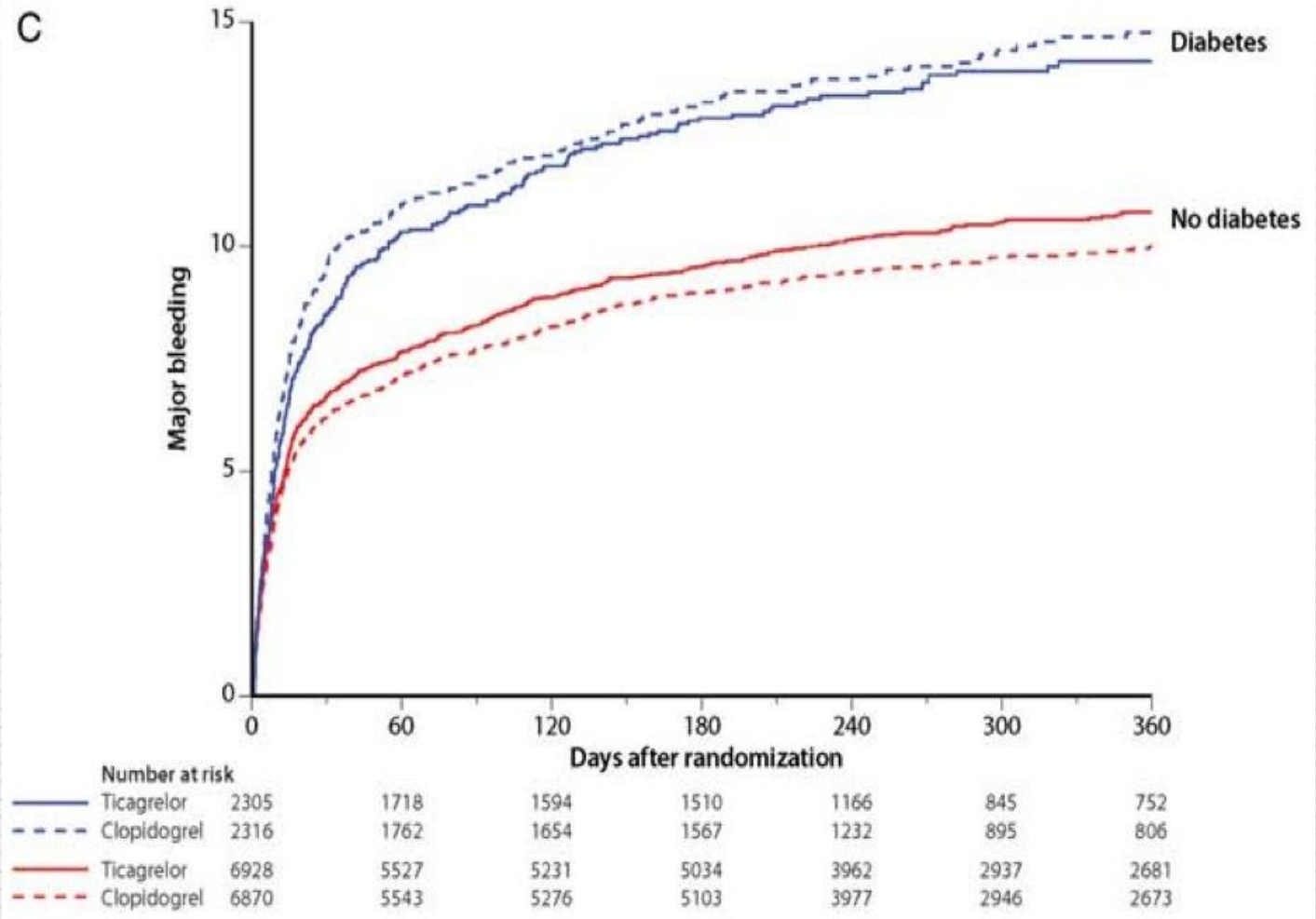
James S et al. European Heart Journal 2010

PLATO (ticagrelor vs. clopidogrel)
Diabetes substudy Total mortality



James S et al. European Heart Journal 2010

PLATO (ticagrelor vs. clopidogrel)
Diabetes substudy Major bleeding



James S et al. European Heart Journal 2010

Different Strokes for Different Folks – *The Folks On Ticagrelor*

- **Age - Not an Issue**
- **Weight – Not an Issue**
- **Prior CVA/TIA – Not an Issue**
- **Diabetes Mellitus**
- **GRACE/TIMI score**
- **CRUSADE bleeding score**
- **Invasive vs Conservative Mgt**
- **Timing of Invasive Mgt**
- **Likelihood of CABG/surgery**
- **Concomitant anticoagulant Rx -???????**
- **Rx compliance**

Different Strokes for Different Folks – *The Folks On Ticagrelor*

- **Age - Not an Issue**
- **Weight – Not an Issue**
- **Prior CVA/TIA – Not an Issue**
- **Diabetes Mellitus**
- **GRACE/TIMI score**
- **CRUSADE bleeding score**
- **Invasive vs Conservative Mgt**
- **Timing of Invasive Mgt**
- **Likelihood of CABG/surgery**
- **Concomitant anticoagulant Rx**
- **Rx compliance**

Procedures and timing*

PLATO Invasive

Procedure	Ticagrelor (n=6,732)	Clopidogrel (n=6,676)
Invasive procedures at index hospitalization, % (n)		
Coronary angiography	**96.8 (6514)**	**96.9 (6471)**
Median (IQR), hours	**0.62 (0.10, 3.70)**	**0.62 (0.12, 3.65)**
PCI during index hospitalization % (n)	**76.7 (5166)**	**77.1 (5148)**
Median (IQR), hours	**0.77 (0.30, 2.75)**	**0.78 (0.32, 2.65)**
UA/NSTEMI – PCI % (n)	**63.8 (1882)**	**64.8 (1854)**
Median (IQR), hours	**2.63 (0.78, 21.10)**	**2.60 (0.87, 21.30)**
STEMI - Primary PCI % (n)	**83.2 (3138)**	**82.7 (3149)**
Median (IQR), hours	**0.47 (0.23, 0.95)**	**0.48 (0.23, 0.95)**
Coronary by-pass surgery pre-discharge % (n)	**5.5 (372)**	**6.1 (410)**
Median (IQR), hours	**117 (47, 216)**	**121 (48, 218)**

* Time between randomization and first procedure

Stent thrombosis

PLATO Invasive

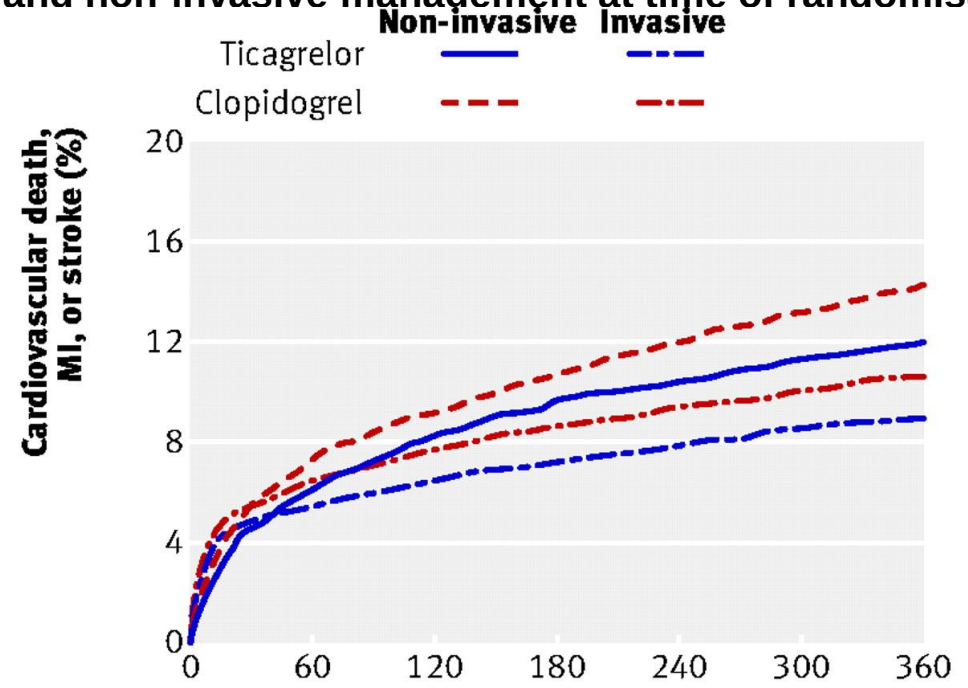
	Ticagrelor (n=6,732)	Clopidogrel (n=6,676)	HR for ticagrelor (95% CI)	p value*
Stent thrombosis, %				
Definite	1.0	1.6	0.62 (0.45–0.85)	0.003
Probable or definite	1.7	2.3	0.72 (0.56–0.93)	0.01
Possible, probable, or definite	2.2	3.1	0.72 (0.58–0.90)	0.003

¶ Evaluated in patients with any stent during the study

Time-at-risk is calculated from the date of first stent insertion in the study or date of randomization

* By univariate Cox model

Fig 3 Cumulative incidence of primary composite of cardiovascular death, myocardial infarction (MI), and stroke in ticagrelor and clopidogrel groups in patients intended for invasive and non-invasive management at time of randomisation.



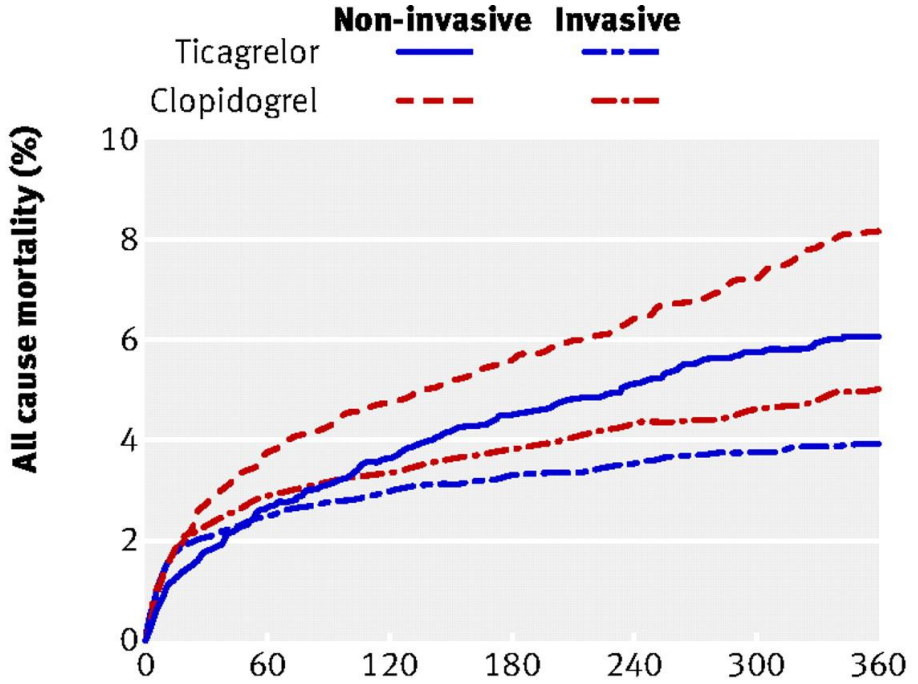
No at risk

Invasive							
Ticagrelor	6732	6236	6134	5972	4889	3735	3048
Clopidogrel	6676	6129	6034	5881	4815	3680	2965
Non-invasive							
Ticagrelor	2601	2392	2326	2247	1854	1426	1099
Clopidogrel	2615	2392	2328	2243	1835	1416	1109

James S K et al. BMJ 2011;342:bmj.d3527

BMJ

Fig 4 Cumulative incidence of total mortality in ticagrelor and clopidogrel groups in patients intended for invasive and non-invasive management at time of randomisation.



No at risk

Invasive							
Ticagrelor	6732	6439	6375	6241	5141	3951	3233
Clopidogrel	6676	6376	6331	6209	5114	3917	3164
Non-invasive							
Ticagrelor	2601	2485	2447	2385	1978	1531	1186
Clopidogrel	2615	2488	2448	2380	1965	1524	1200

James S K et al. BMJ 2011;342:bmj.d3527

Different Strokes for Different Folks – *The Folks On Ticagrelor*

- **Age - Not an Issue**
- **Weight – Not an Issue**
- **Prior CVA/TIA – Not an Issue**
- **Diabetes Mellitus**
- **GRACE/TIMI score**
- **CRUSADE bleeding score**
- **Invasive vs Conservative Mgt**
- **Timing of Invasive Mgt**
- **Likelihood of CABG/surgery**
- **Concomitant anticoagulant Rx**
- **Rx compliance**

PLATO study design

PLATO

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(addition[illegible]0 mg pre-PCI)

6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack

Holter monitoring & Bradycardia related events

PLATO

Holter monitoring at first week	Ticagrelor (n=1,451)	Clopidogrel (n=1,415)	p value
Ventricular pauses ≥3 seconds, %	5.8	3.6	0.01
Ventricular pauses ≥5 seconds, %	2.0	1.2	0.10

Holter monitoring at 30 days	Ticagrelor (n= 985)	Clopidogrel (n=1,006)	p value
Ventricular pauses ≥3 seconds, %	2.1	1.7	0.52
Ventricular pauses ≥5 seconds, %	0.8	0.6	0.60

Bradycardia-related event, %	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value
Pacemaker Insertion	0.9	0.9	0.87
Syncope	1.1	0.8	0.08
Bradycardia	4.4	4.0	0.21
Heart block	0.7	0.7	1.00

Other findings

PLATO

All patients	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value*
Dyspnoea, %			
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001
Neoplasms arising during treatment, %			
Any	1.4	1.7	0.17
Malignant	1.2	1.3	0.69
Benign	0.2	0.4	0.02

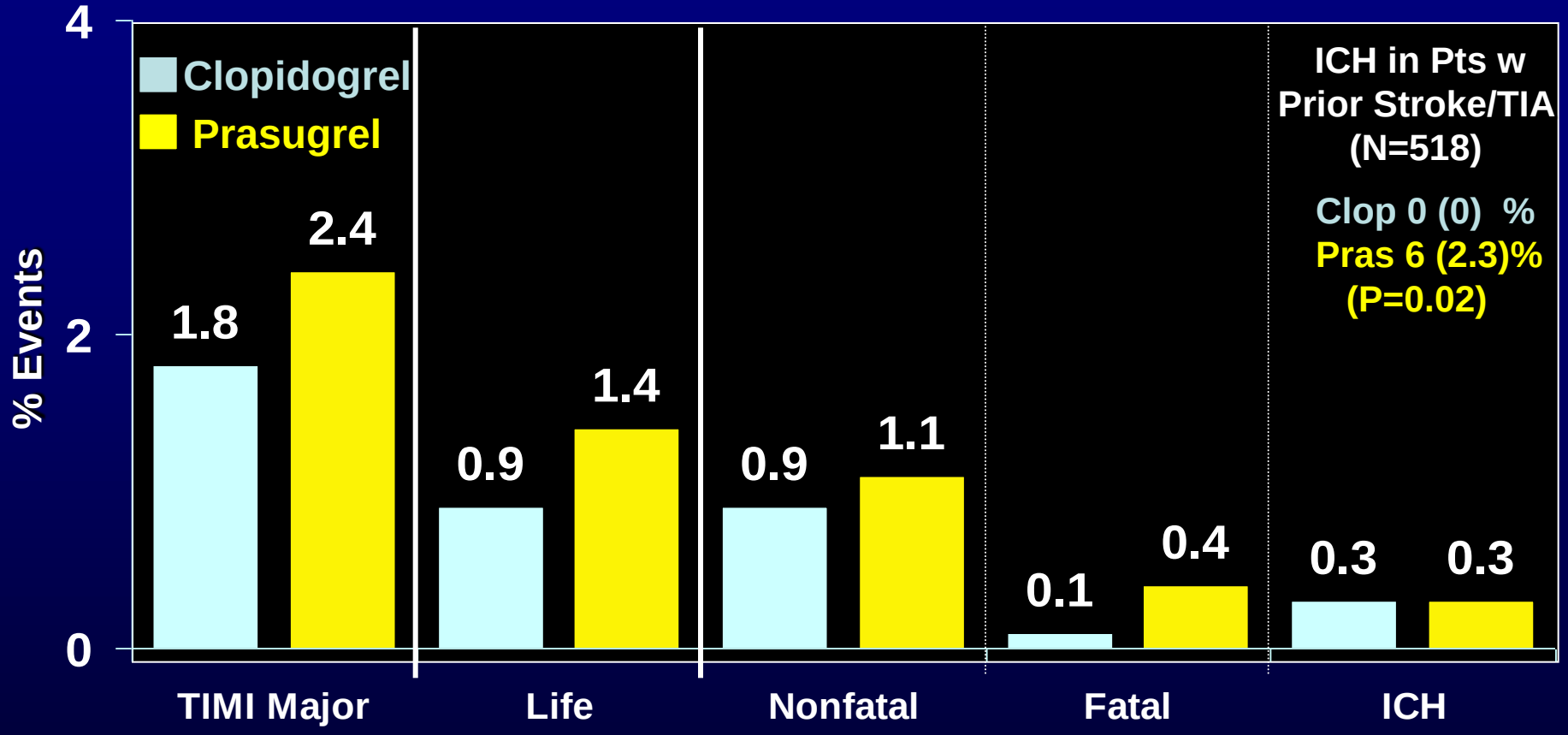
*p values were calculated using Fischer's exact test

Different Strokes for Different Folks – *The Folks On Prasugrel*

- **Age - >75 yo**
- **Weight – <60Kg**
- **Prior CVA/TIA – Contraindicated**
- **Diabetes Mellitus**
- **GRACE/TIMI score**
- **CRUSADE bleeding score**
- **Invasive vs Conservative Mgt – Only for PCI pts**
- **Timing of Invasive Mgt**
- **Likelihood of CABG/surgery - Only for PCI pts**
- **Concomitant anticoagulant Rx**
- **Rx compliance**

TRITON TIMI·38

Bleeding Events
Safety Cohort
(N=13,457)



ARD 0.6%
HR 1.32
P=0.03
NNH=167

ARD 0.5%
HR 1.52
P=0.01

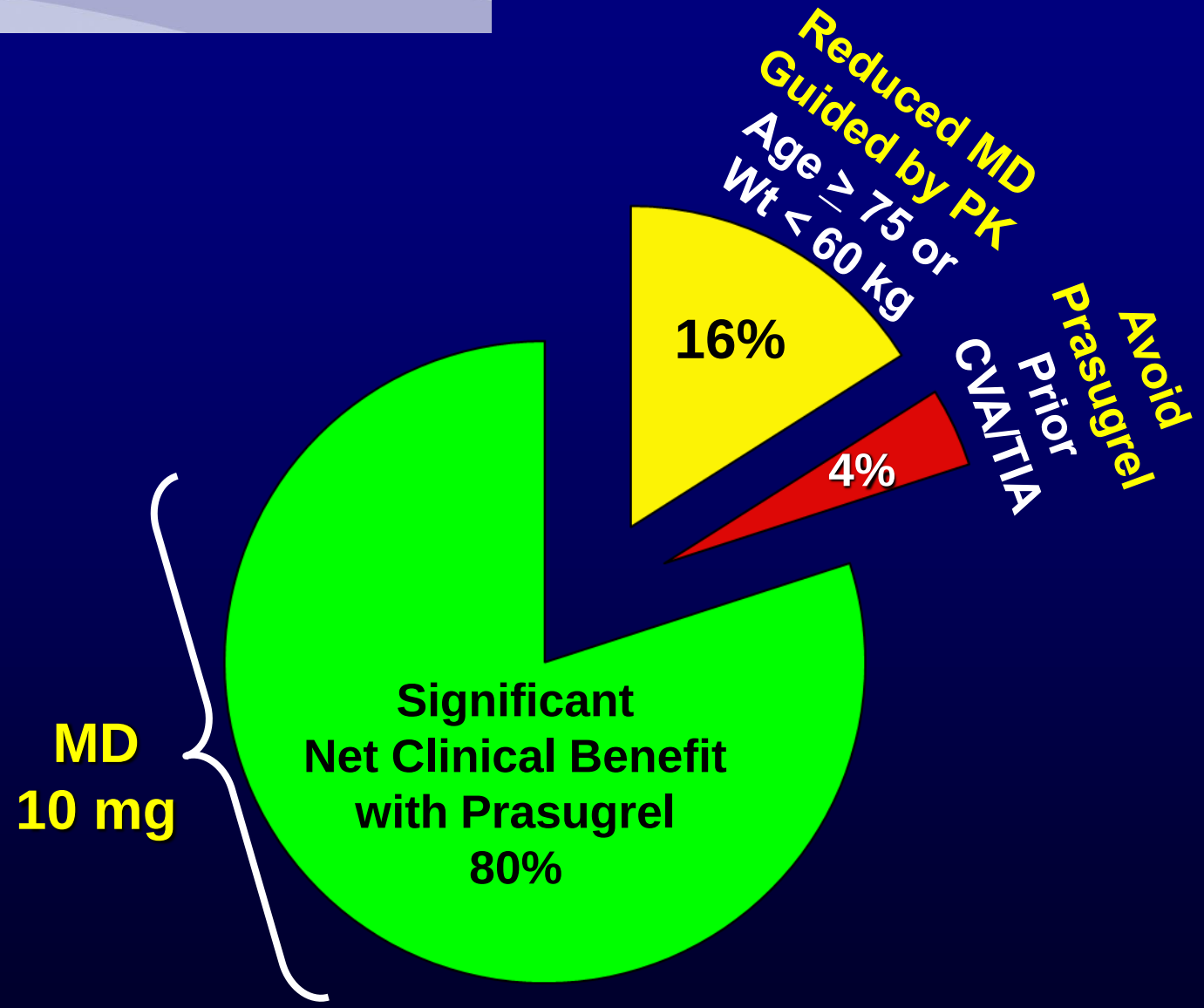
ARD 0.2%
P=0.23

ARD 0.3%
P=0.002

ARD 0%
P=0.74

TRITON TIMI·38

Bleeding Risk Subgroups
Therapeutic Considerations



Prasugrel vs. Clopidogrel for Acute Coronary Syndromes Patients Managed without Revascularization — the TRILOGY ACS trial

On behalf of the TRILOGY ACS Investigators

Duke Clinical Research Institute

www.clinicaltrials.gov Identifier: NCT00699998

TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

Randomization Stratified by:
Age, Country, Prior Clopidogrel Treatment
(Primary analysis cohort — Age < 75 years)

Median Time to Enrollment = 4.5 Days

Medical Management Decision ≤72 hrs
(No prior clopidogrel given) — 4% of total

- **Clopidogrel[1]** 300 mg LD + 75 mg MD
- **Prasugrel[1]** 30 mg LD + 5 or 10 mg MD

Medical Management Decision ≤ 10 days
(Clopidogrel started ≤ 72 hrs in-hospital OR on chronic clopidogrel) — 96% of total

- **Clopidogrel[1]** 75 mg MD
- **Prasugrel[1]** 5 or 10 mg MD

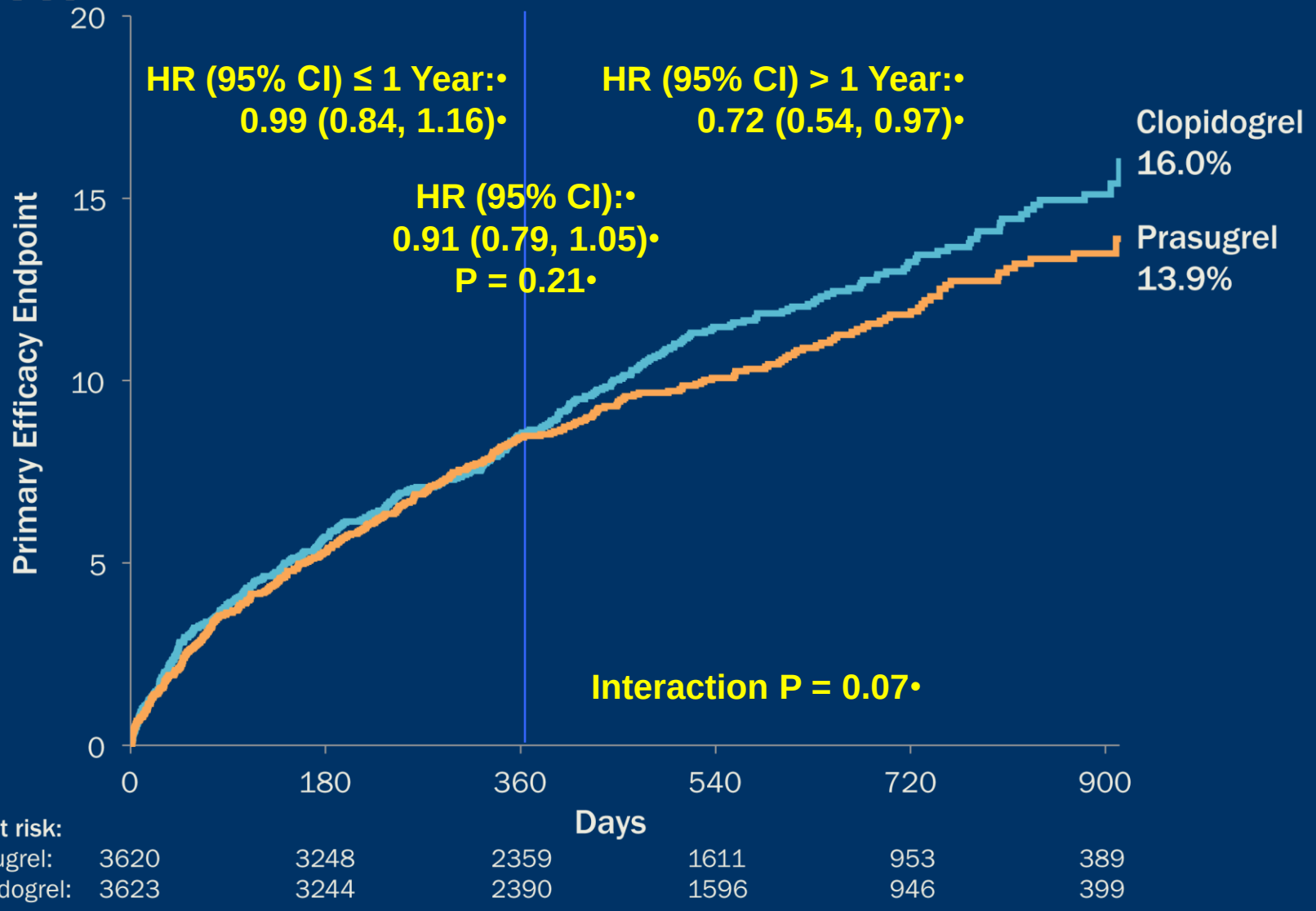
Minimum Rx Duration: 6 months; Maximum Rx Duration: 30 months

Primary Efficacy Endpoint: CV Death, MI, Stroke

All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 .1 years, 5 mg MD of prasugrel was given. Adapted from Chin CT et al. *Am Heart J* 2010;160:16-22.e1.

Primary Efficacy Endpoint to 30 Months

(Age < 75 years)



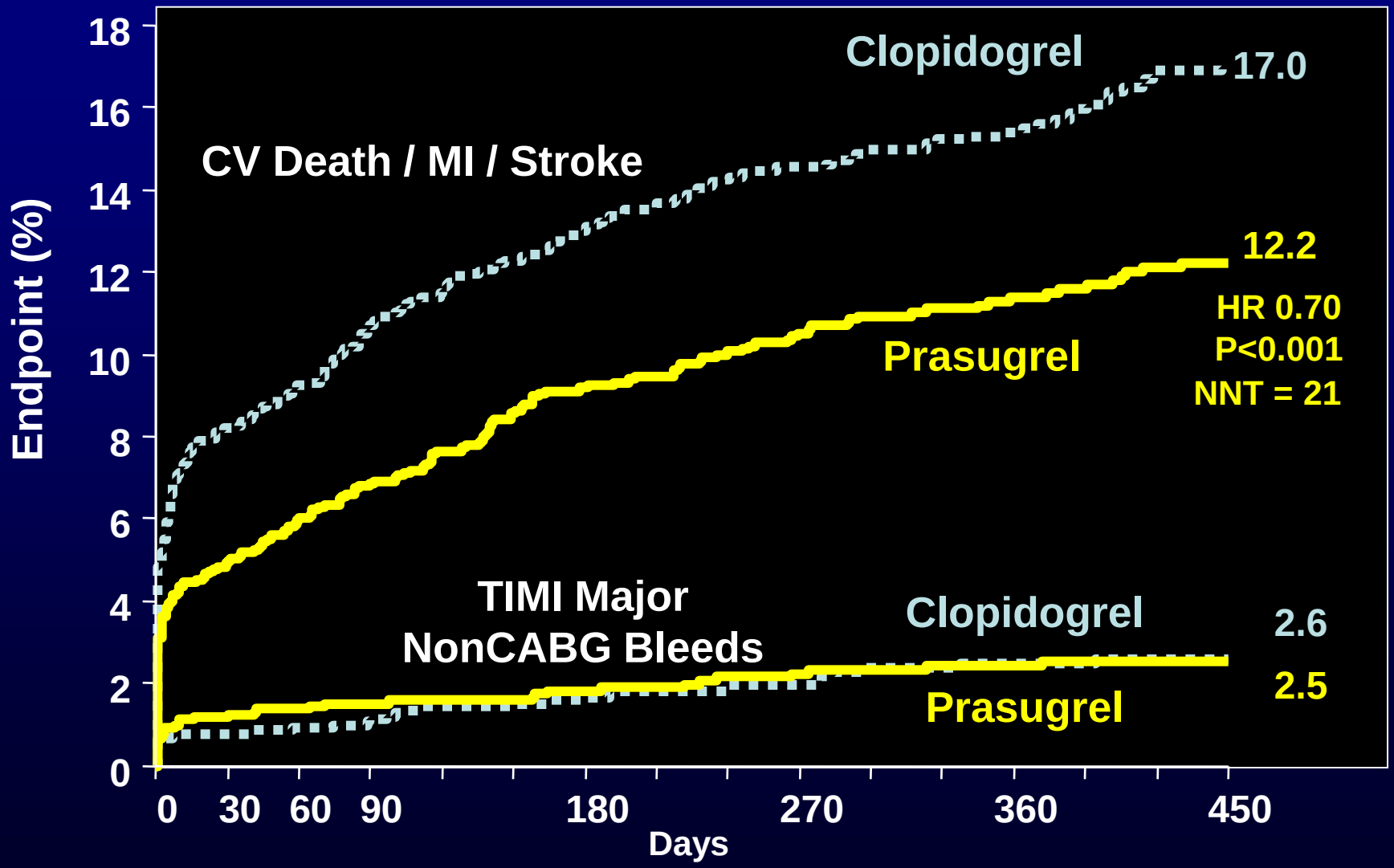
Different Strokes for Different Folks – *The Folks On Prasugrel*

- Age
- Weight
- Prior CVA/TIA
- Diabetes Mellitus
- GRACE/TIMI score
- CRUSADE bleeding score
- Invasive vs Conservative Mgt
- Timing of Invasive Mgt
- Likelihood of CABG/surgery
- Concomitant anticoagulant Rx
- Rx compliance

TRITON TIMI·38

Diabetic Subgroup

N=3146



Kaplan–Meier curves for prasugrel versus clopidogrel

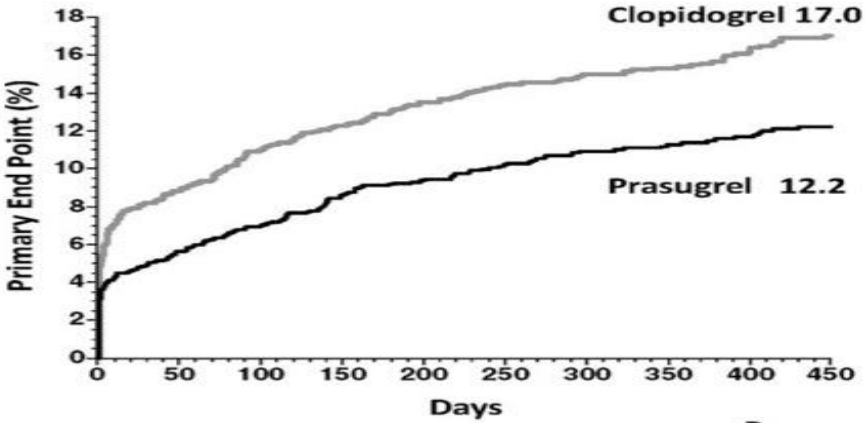
Patients with DM vs no DM from the TRITON-TIMI 38 trial

Primary End Point

A

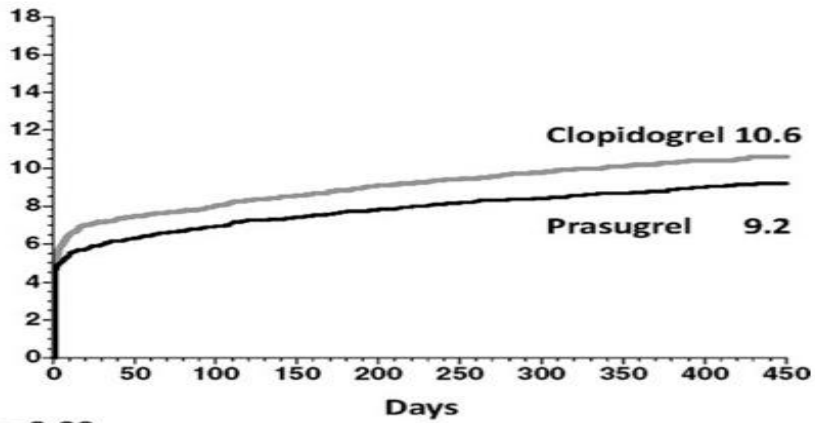
DM

HR 0.70 (0.58-0.85), P<0.001



No DM

HR 0.86 (0.76-0.98), P = 0.02



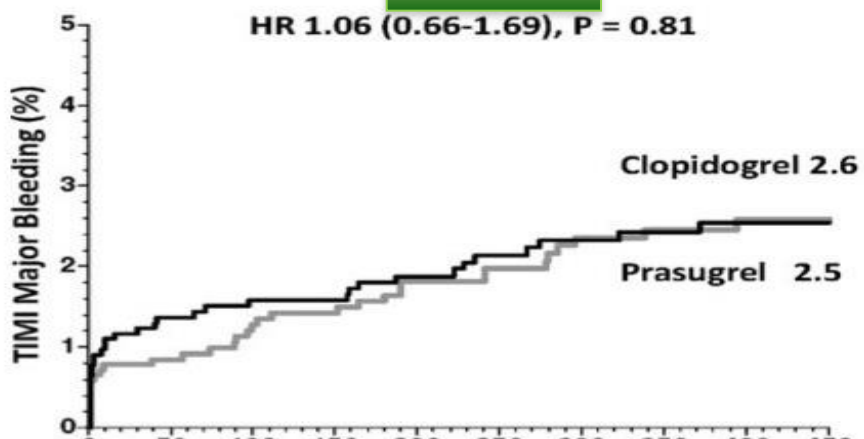
$P_{interaction} = 0.09$

TIMI Major Bleeding

D

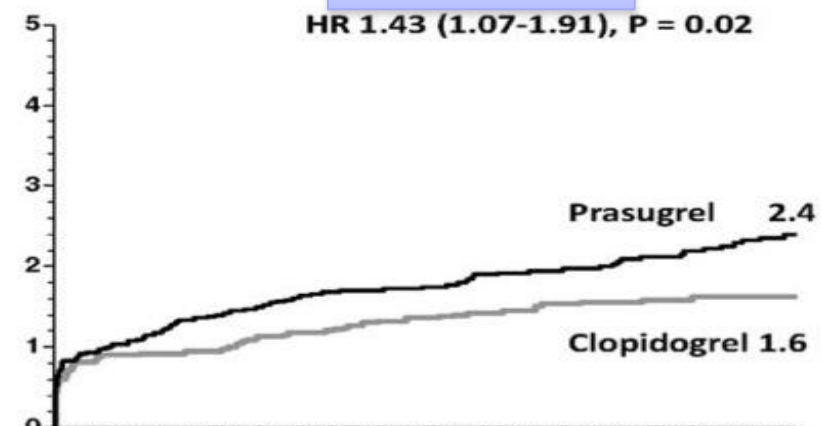
DM

HR 1.06 (0.66-1.69), P = 0.81



No DM

HR 1.43 (1.07-1.91), P = 0.02



$P_{interaction} = 0.29$

Different Strokes for Different Folks – *The Folks On Prasugrel*

- **Age**
- **Weight**
- **Prior CVA/TIA**
- **Diabetes Mellitus**
- **GRACE/TIMI score**
- **CRUSADE bleeding score**
- **Invasive vs Conservative Mgt**
- **Timing of Invasive Mgt**
- **Likelihood of CABG/surgery - ???!!!**
- **Concomitant anticoagulant Rx - ??????**
- **Rx compliance – Probably not an issue**

Conclusion

- **P2Y12 receptor blockers indicated for NSTE-ACS pts**
- **Choice depends on clinical scenario, baseline demographic and clinical characteristics, overall treatment strategy, and bleeding risk**