$P2Y_{12}$ Receptor Inhibitors After Percutaneous Coronary Syndromes – Understanding the 2016 ACC/AHA Antiplatelet Guideline Updates?

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DE UNIVERSITE D' OTTAWA

Disclosure Statement

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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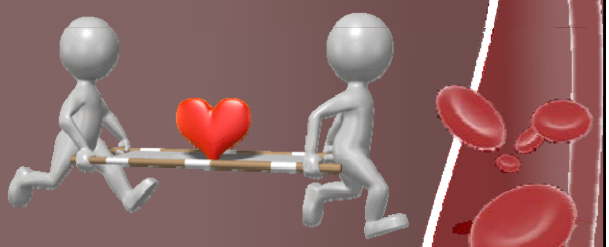
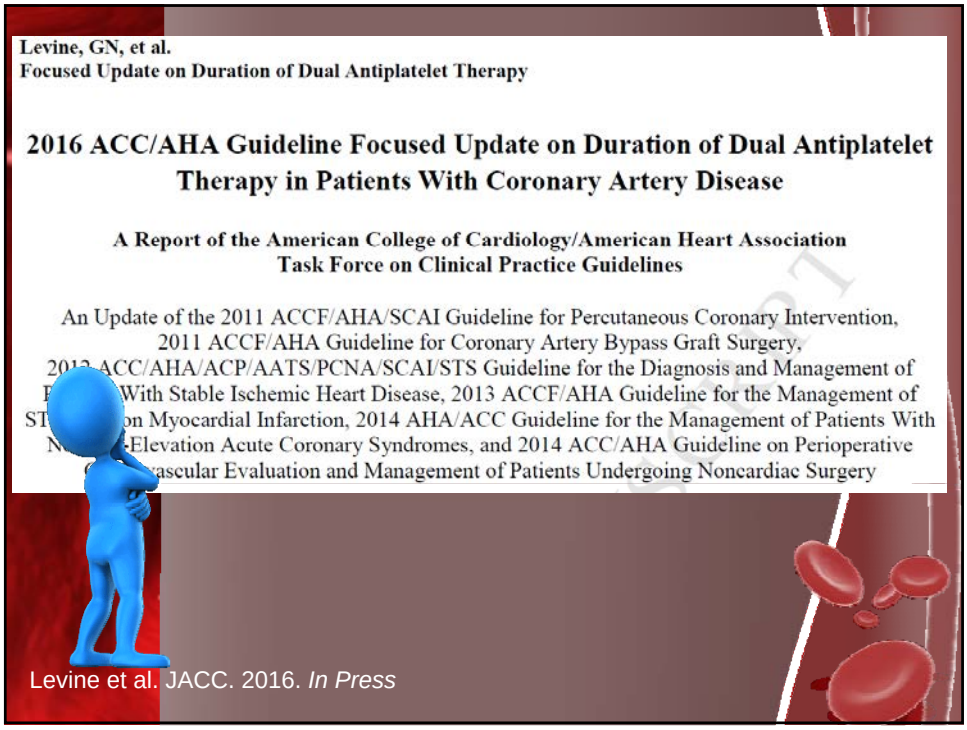
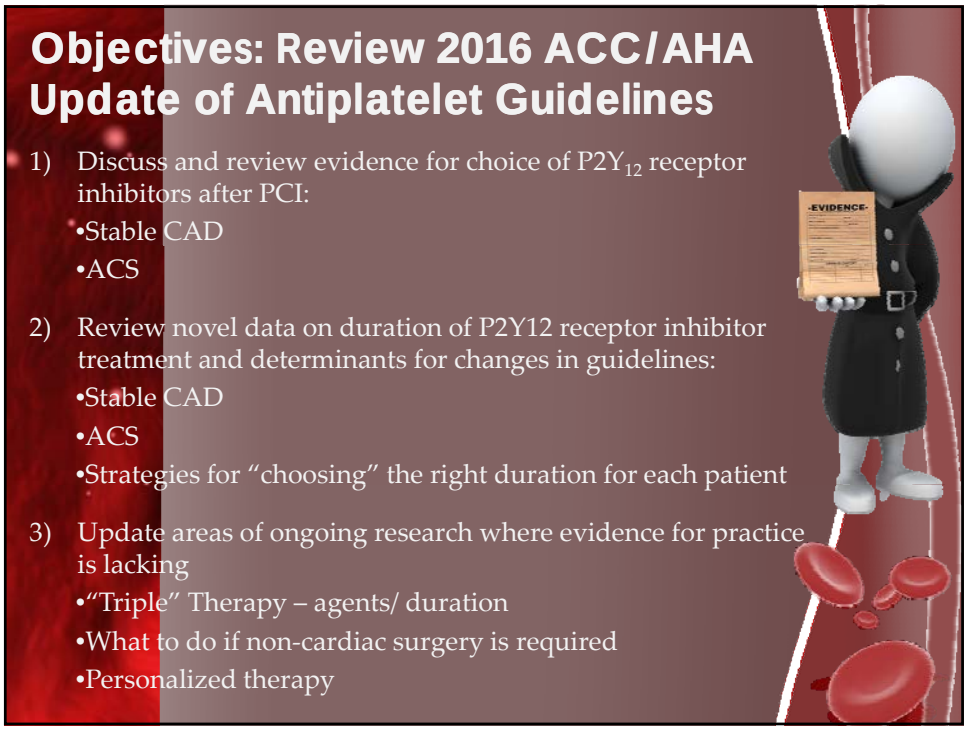
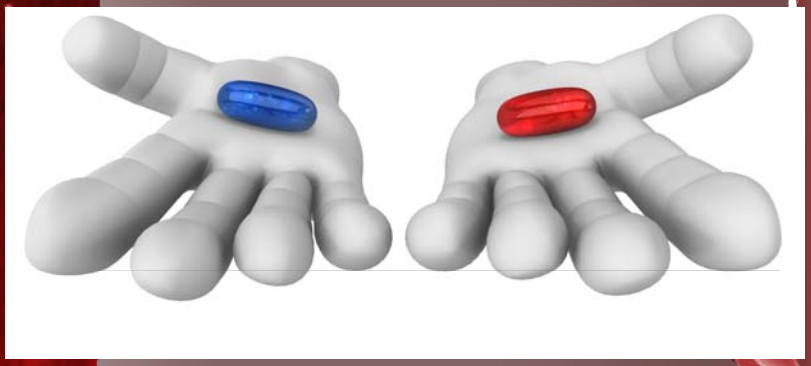



Levine, GN, et al.
Focused Update on Duration of Dual Antiplatelet Therapy
2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease
A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines
An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery,
With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of
on Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With
Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative
ascular Evaluation and Management of Patients Undergoing Noncardiac Surgery
Levine et al. JACC. 2016. In Press


Objectives: Review 2016 ACC/AHA Update of Antiplatelet Guidelines
1) Discuss and review evidence for choice of $P2Y_{12}$ receptor inhibitors after PCI:
•Stable CAD
•ACS
2) Review novel data on duration of P2Y12 receptor inhibitor treatment and determinants for changes in guidelines:
•Stable CAD
•ACS
•Strategies for "choosing" the right duration for each patient
3) Update areas of ongoing research where evidence for practice is lacking
•"Triple" Therapy – agents/ duration
•What to do if non-cardiac surgery is required
•Personalized therapy
EVIDENCE

Choosing the Right $P2Y_{12}$ Inhibitor…



The P2Y12 Receptor Inhibitors:

Clopidogrel

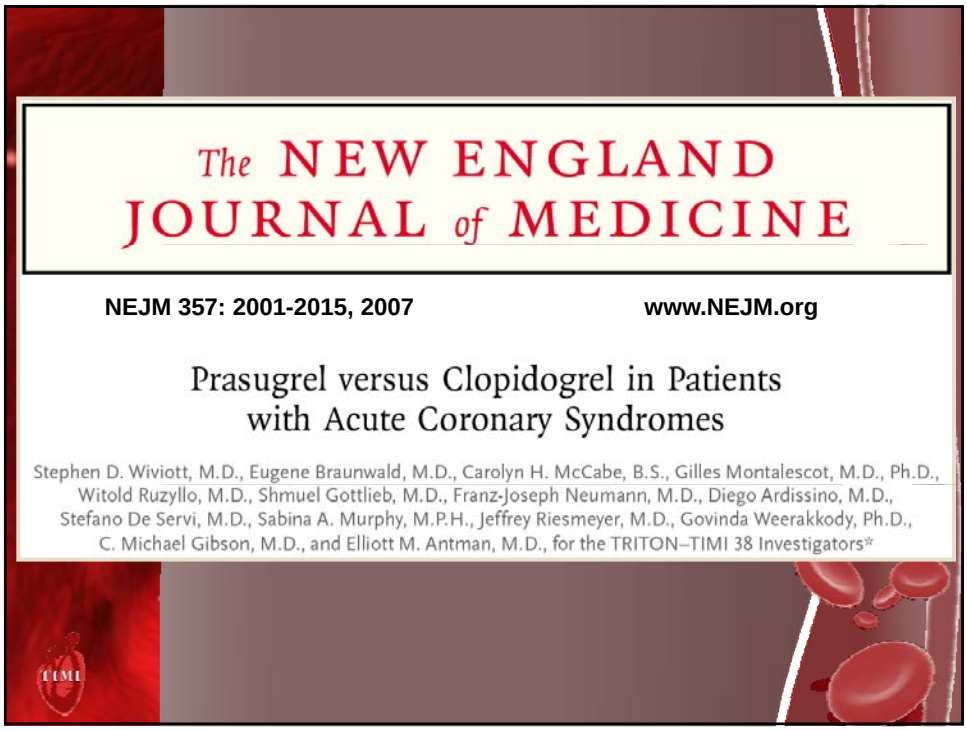
- Thienopyridine
- 2 step biotransformation
- Generic

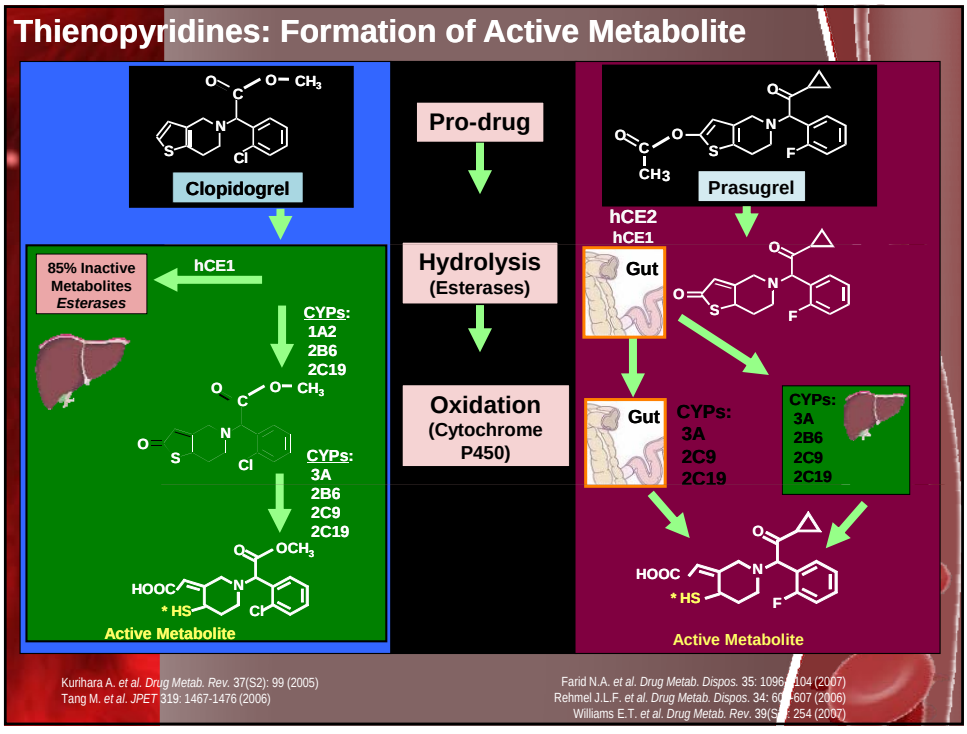
Prasugrel

- Thienopyridine
- 1 step biotransformation

Ticagrelor

- Cyclo-pentyl-triazolo pyrimidine
- Direct and reversible P2Y12 inhibitor


The NEW ENGLAND JOURNAL of MEDICINE
NEJM 357: 2001-2015, 2007
www.NEJM.org
Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes
Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*


Thienopyridines: Formation of Active Metabolite
Clopidogrel
Pro-drug
Prasugrel
hCE2
hCE1
Gut
85% Inactive Metabolites
Esterases
hCE1
Hydrolysis
(Esterases)
CYPs:
1A2
2B6
2C19
CYPs:
3A
2B6
2C9
2C19
Oxidation
(Cytochrome
P450)
Gut
CYPs:
3A
2C9
2C19
CYPs:
3A
2B6
2C9
2C19
HOOC
* HS
Active Metabolite
Active Metabolite
Kurihara A. et al. Drug Metab. Rev. 37(S2): 99 (2005)
Tang M. et al. JPET 319: 1467-1476 (2006)
Farid N.A. et al. Drug Metab. Dispos. 35: 1096-1104 (2007)
Rehmel J.L.F. et al. Drug Metab. Dispos. 34: 600-607 (2006)
Williams E.T. et al. Drug Metab. Rev. 39(S1): 254 (2007)

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ N= 13,600

Double-blind

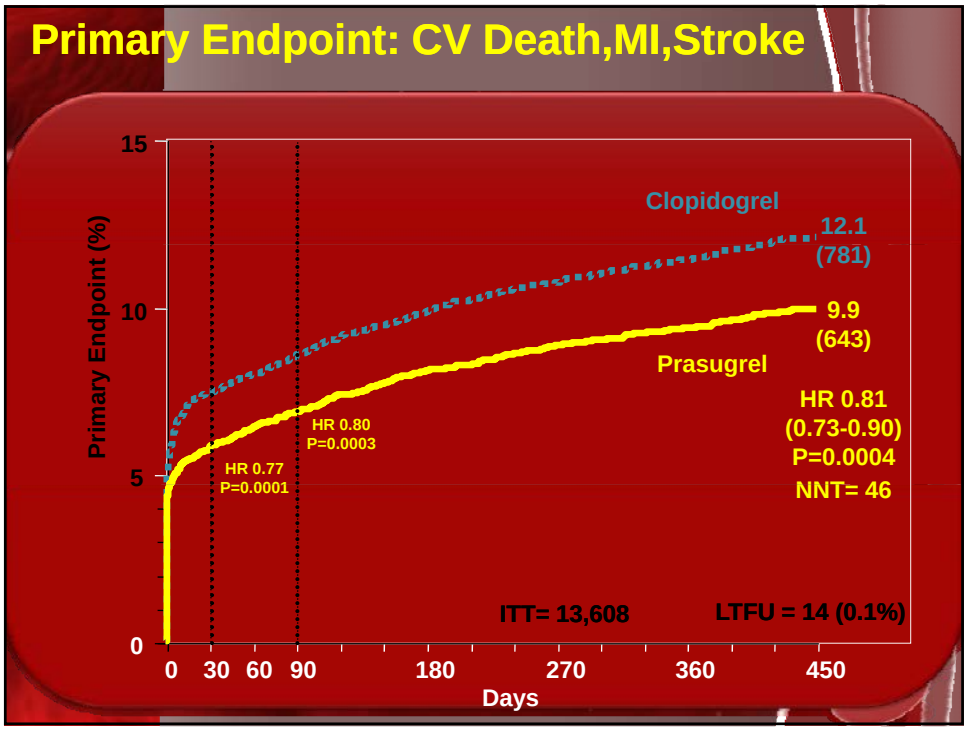
CLOPIDOGREL	PRASUGREL
300 mg LD/ 75 mg MD	60 mg LD/ 10 mg MD

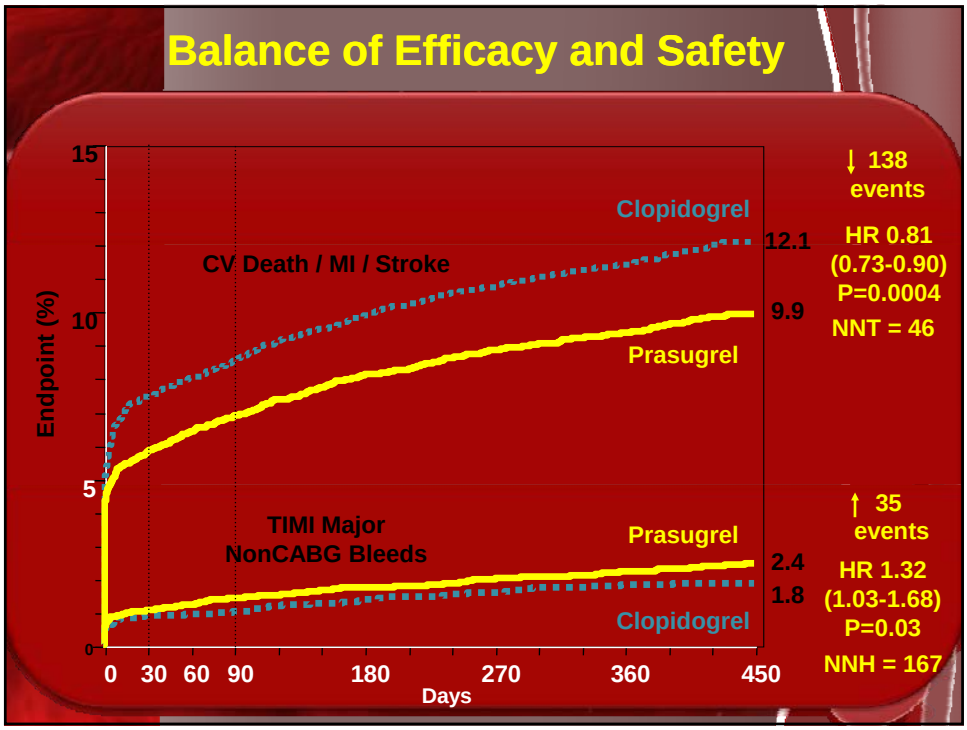
Median duration of therapy - 12 months

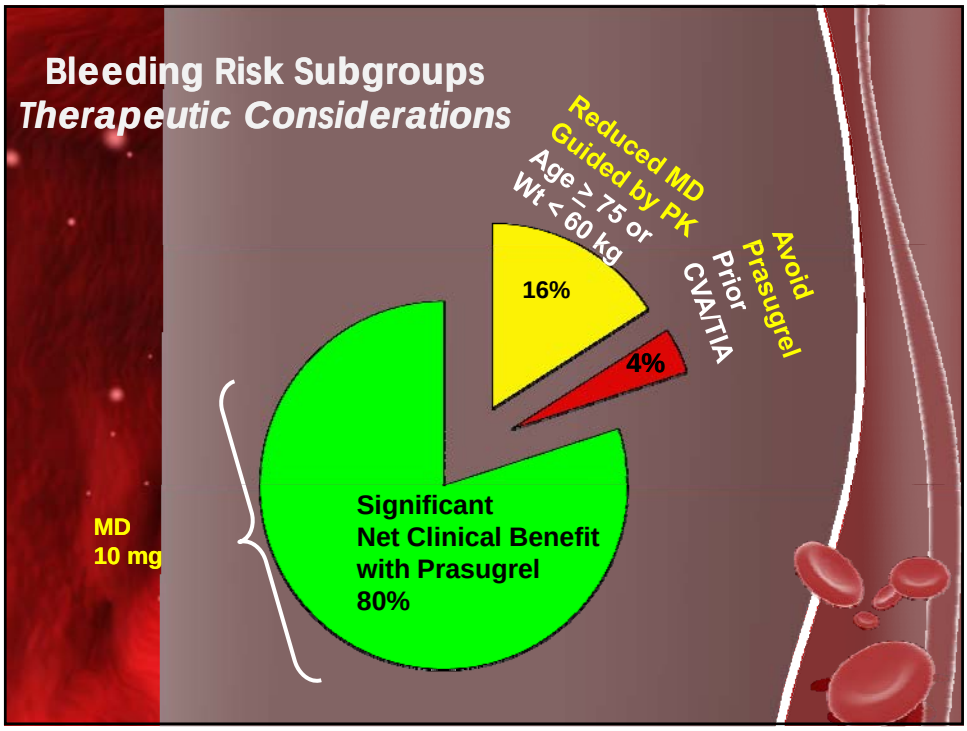
1º endpoint:	CV death, MI, Stroke
2º endpoints:	CV death, MI, Stroke, Rehosp-Rec Isch
	CV death, MI, UTVR
	Stent Thrombosis (ARC definite/prob.)
Safety endpoints:	TIMI major bleeds, Life-threatening bleeds
Key Substudies:	Pharmacokinetic, Genomic

Enrollment Criteria

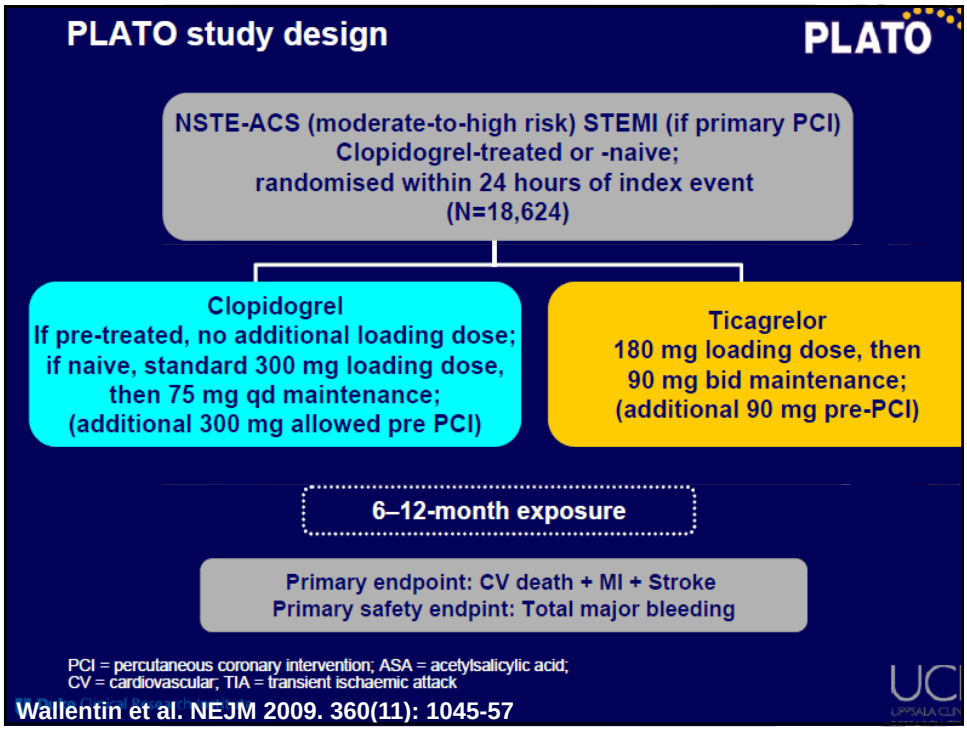
- **Inclusion Criteria**
  - Planned PCI for :
    - *Known Anatomy*
      - Mod-High Risk UA/NSTEMI (TRS ≥ 3)
      - STEMI: ≤ 14 days (ischemia or Rx strategy)
      - STEMI: Primary PCI
- **Major Exclusion Criteria**:
  - Severe comorbidity
  - Increased bleeding risk
  - Prior hemorrhagic stroke or any stroke ≤ 3 mos
  - Any thienopyridine within 5 days
  - No exclusion for advanced age or renal function

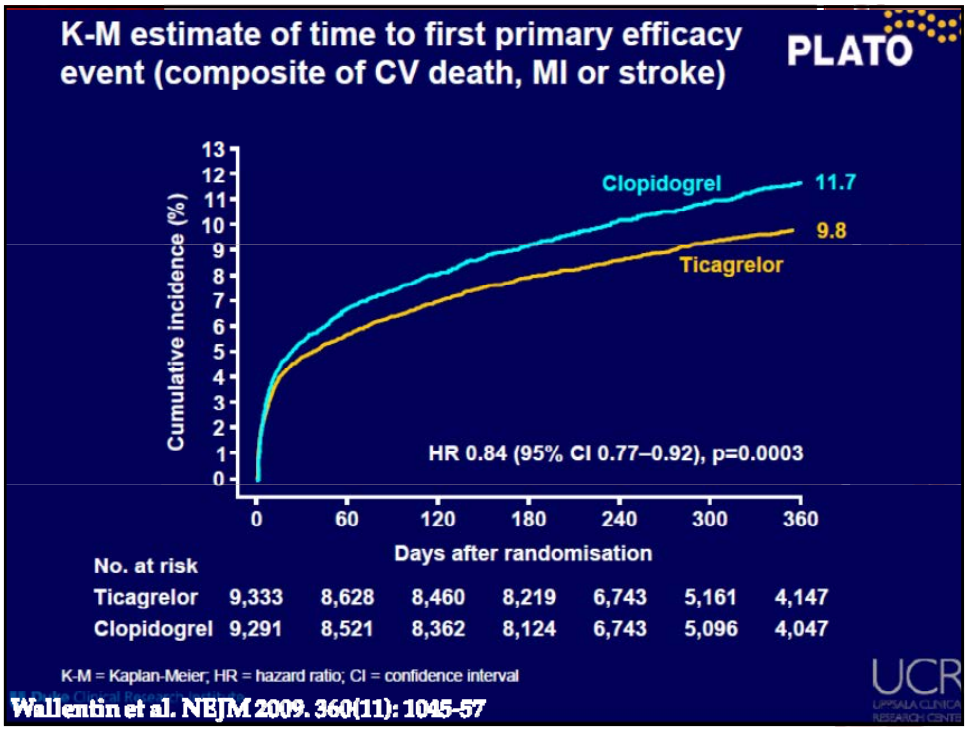

Primary Endpoint: CV Death,MI,Stroke
Primary Endpoint (%)
15
10
5
0
Clopidogrel
12.1
(781)
9.9
(643)
Prasugrel
HR 0.81
(0.73-0.90)
P=0.0004
NNT= 46
HR 0.80
P=0.0003
HR 0.77
P=0.0001
ITT= 13,608
LTFU = 14 (0.1%)
0 30 60 90 180 270 360 450
Days


Balance of Efficacy and Safety
Endpoint (%)
15
10
5
0
CV Death / MI / Stroke
Clopidogrel
12.1
9.9
Prasugrel
↓ 138
events
HR 0.81
(0.73-0.90)
P=0.0004
NNT = 46
TIMI Major
NonCABG Bleeds
Prasugrel
2.4
1.8
Clopidogrel
↑ 35
events
HR 1.32
(1.03-1.68)
P=0.03
NNH = 167
0 30 60 90 180 270 360 450
Days


Bleeding Risk Subgroups
Therapeutic Considerations
Reduced MD
Guided by PK
Age ≥ 75 or
Wt < 60 kg
16%
Avoid
Prasugrel
Prior
CVA/TIA
4%
Significant
Net Clinical Benefit
with Prasugrel
80%
MD
10 mg


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes
Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*
Wallentin et al. NEJM 2009. 360(11): 1045-57


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;
(additional 90 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
Wallentin et al. NEJM 2009. 360(11): 1045-57


K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)
PLATO
Cumulative incidence (%)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Clopidogrel
11.7
9.8
Ticagrelor
HR 0.84 (95% CI 0.77–0.92), p=0.0003
0
60
120
180
240
300
360
Days after randomisation
No. at risk
Ticagrelor 9,333 8,628 8,460 8,219 6,743 5,161 4,147
Clopidogrel 9,291 8,521 8,362 8,124 6,743 5,096 4,047
K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval
Wallentin et al. NEJM 2009. 360(11): 1045-57

Hierarchical testing major efficacy endpoints

PLATO

All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (95% CI)	p value
Primary objective, n (%)				
CV death + MI + stroke	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	<0.001
Secondary objectives, n (%)				
Total death + MI + stroke	901 (10.2)	1,065 (12.3)	0.84 (0.77–0.92)	<0.001
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	1,290 (14.6)	1,456 (16.7)	0.88 (0.81–0.95)	<0.001
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.005
CV death	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.22
Total death	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	<0.001

The percentages are K-M estimates of the rate of the endpoint at 12 months.

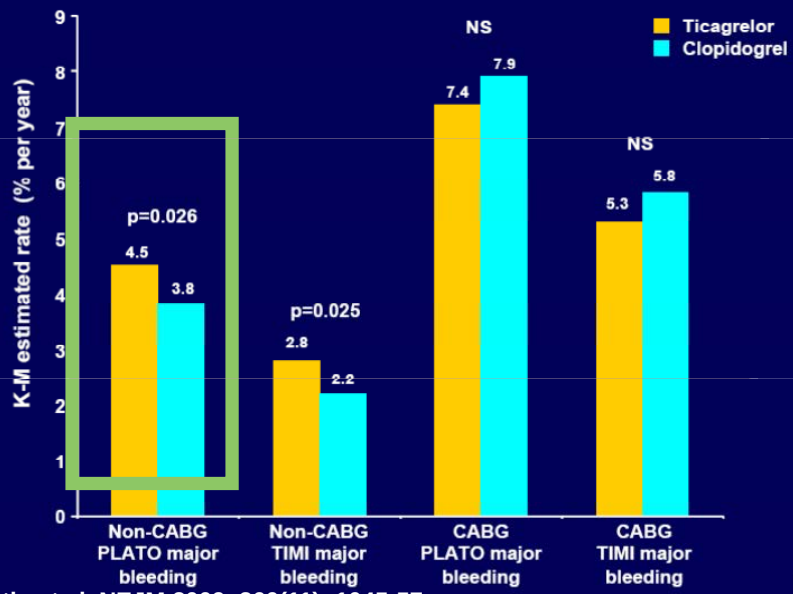
Duke Clinical Research Institute

UCR Uppsala Clinical Research Center

Wallentin et al. NEJM 2009. 360(11): 1045-57

Non-CABG and CABG-related major bleeding

PLATO



Wallentin et al. NEJM 2009. 360(11): 1045-57

UCR

Specific $P2Y_{12}$ Inhibitor: Recommendations

COR	LOE	Recommendations
IIa	B-R	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation and in patients with NSTE-ACS treated with medical therapy alone (without revascularization), it is reasonable to use ticagrelor in preference to clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy (53,71,72).
IIa	B-R	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy (54,55).
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA (54).

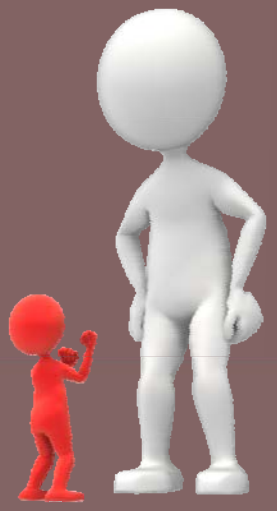
Levine et al. JACC. 2016. *In Press*

A few reminders…

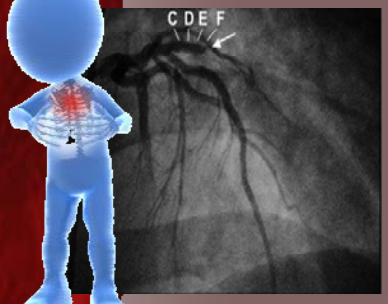
COR	LOE	Recommendation
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended (56-60,75-78).

Levine et al. JACC. 2016. *In Press*

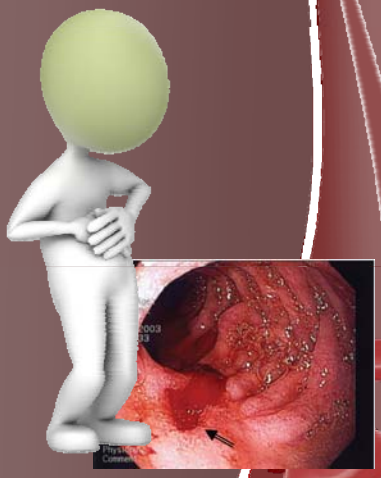
Should We Change the Duration of Therapy?



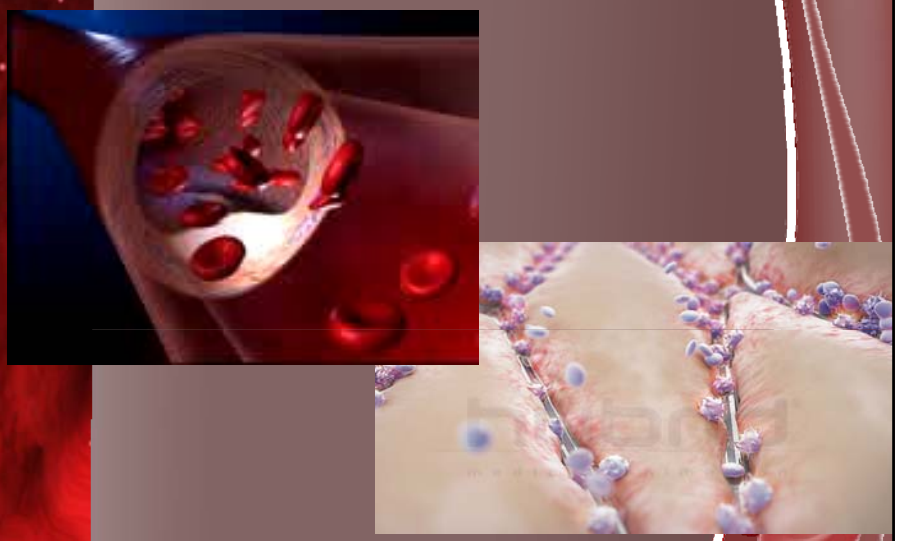
Which patient is worse?



Versus

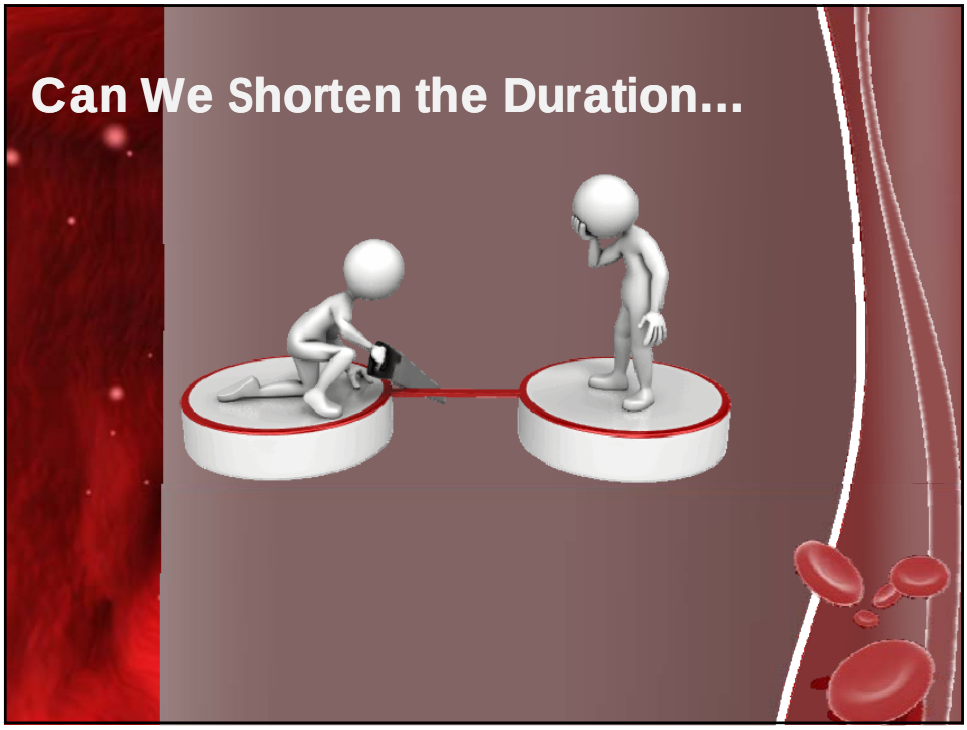


What are we trying to prevent with long term therapy?



The "Ground Rules" of the guidelines…

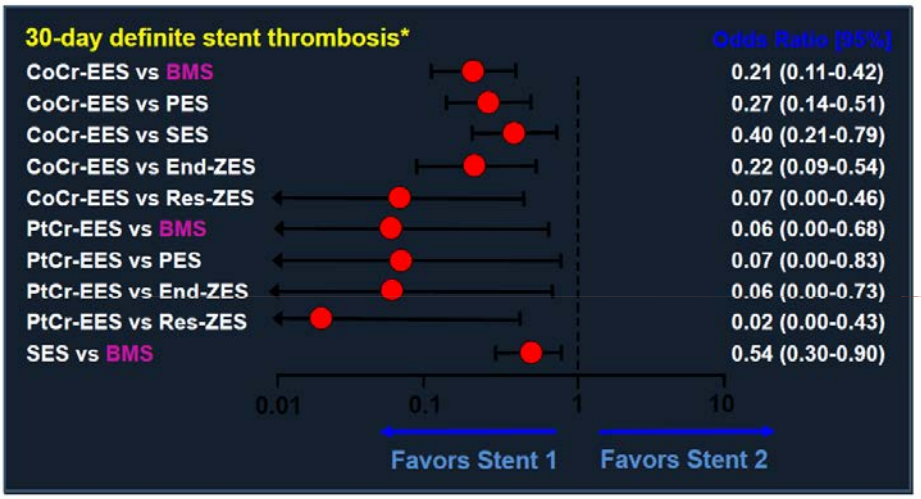
- Evaluate 11 new studies (predominant "novel" generation DES), where duration of DAPT was assessed
- The term "DAPT" refers to combination of aspirin and any one of the $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, ticagrelor)
- Recommendations are taken with the assumptions on patient not having an indication for oral anticoagulant therapy



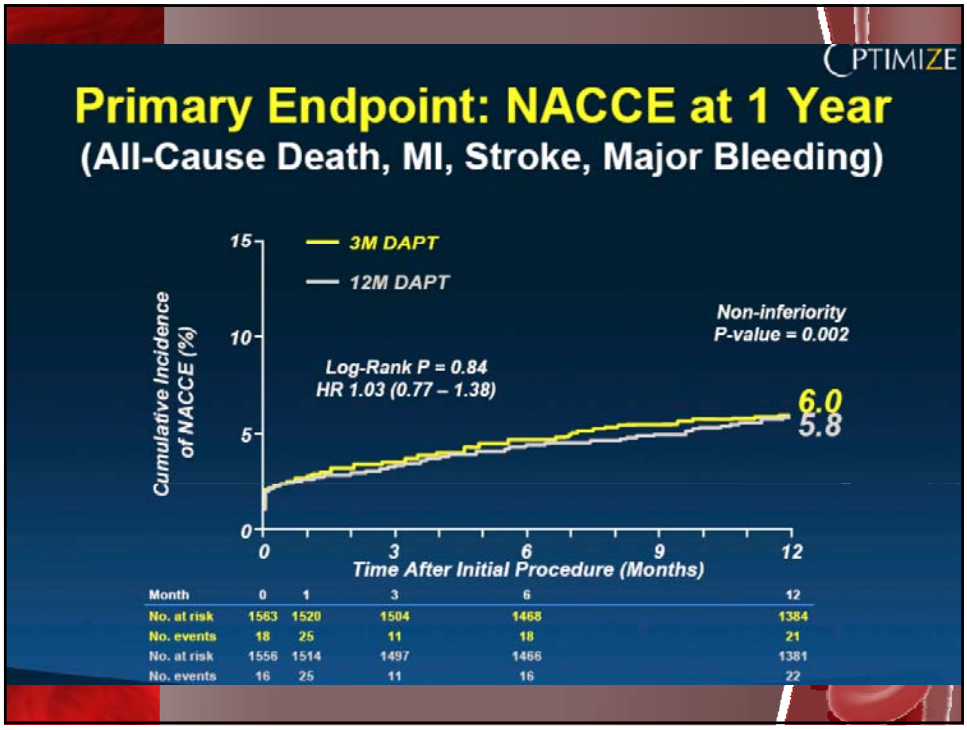
Stent Thrombosis Network Meta-analysis

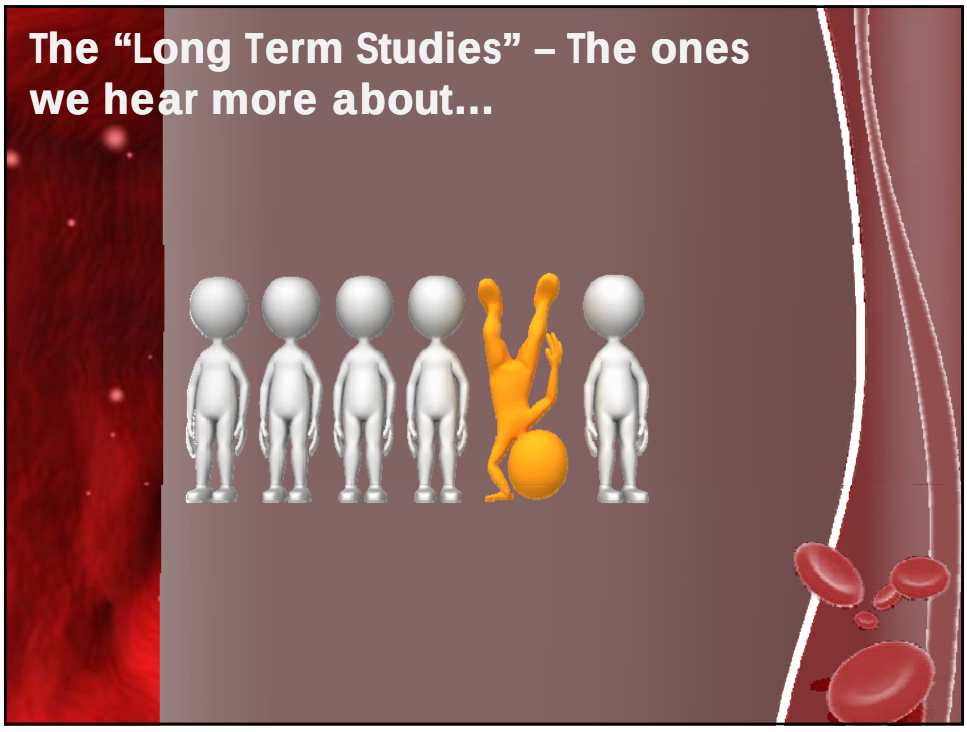
Primary EP: ARC Definite ST (FU through 2 years)

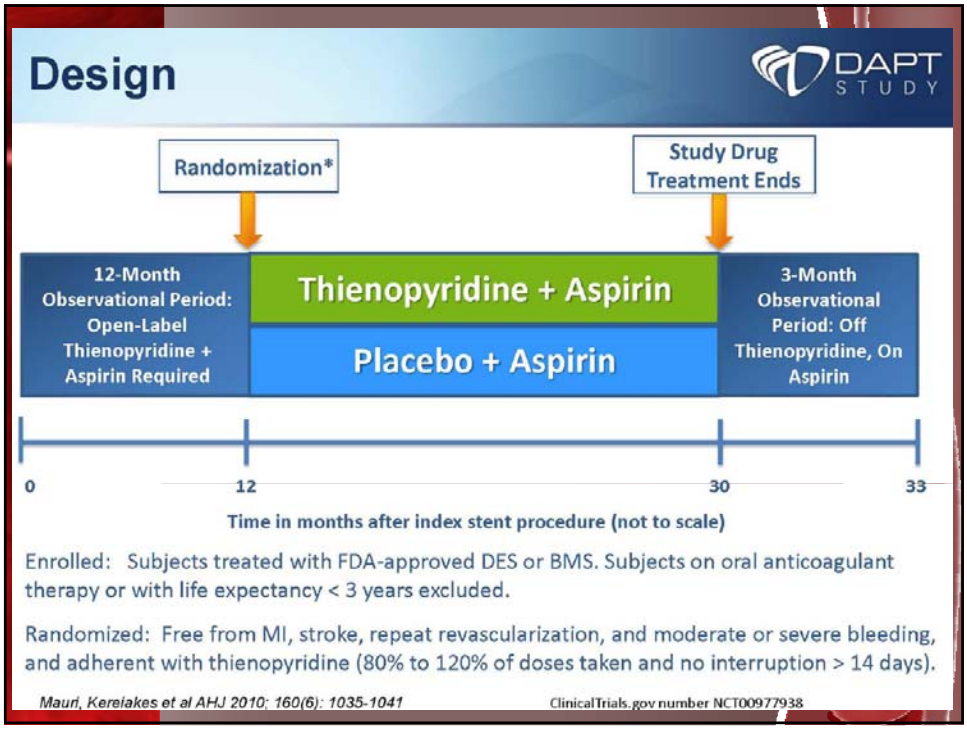
49 RCTs, 50,844 pts

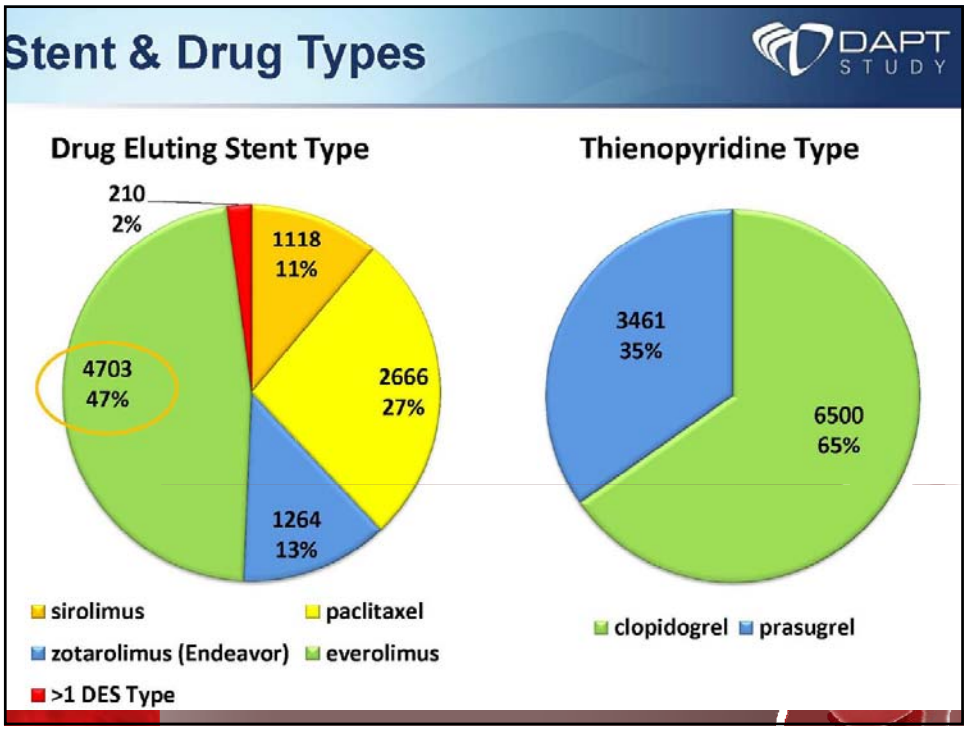


Palmerini T et al. *Lancet* 2012


OPTIMIZE
Primary Endpoint: NACCE at 1 Year
(All-Cause Death, MI, Stroke, Major Bleeding)
3M DAPT
12M DAPT
Cumulative Incidence of NACCE (%)
Non-inferiority P-value = 0.002
Log-Rank P = 0.84
HR 1.03 (0.77 – 1.38)
6.0
5.8
15
10
5
0
0
3
6
9
12
Time After Initial Procedure (Months)
Month 0 1 3 6 12
No. at risk 1563 1520 1504 1468 1384
No. events 18 25 11 18 21
No. at risk 1556 1514 1497 1466 1381
No. events 16 25 11 16 22


The "Long Term Studies" – The ones we hear more about...


Design
DAPT STUDY
Randomization*
Study Drug Treatment Ends
12-Month Observational Period: Open-Label Thienopyridine + Aspirin Required
Thienopyridine + Aspirin
Placebo + Aspirin
3-Month Observational Period: Off Thienopyridine, On Aspirin
0
12
30
33
Time in months after index stent procedure (not to scale)
Enrolled: Subjects treated with FDA-approved DES or BMS. Subjects on oral anticoagulant therapy or with life expectancy < 3 years excluded.
Randomized: Free from MI, stroke, repeat revascularization, and moderate or severe bleeding, and adherent with thienopyridine (80% to 120% of doses taken and no interruption > 14 days).
Mauri, Kereiakes et al AHJ 2010; 160(6): 1035-1041
ClinicalTrials.gov number NCT00977938


Stent & Drug Types
DAPT STUDY
Drug Eluting Stent Type
210
2%
1118
11%
2666
27%
1264
13%
4703
47%
sirolimus
paclitaxel
zotarolimus (Endeavor)
everolimus
>1 DES Type
Thienopyridine Type
3461
35%
6500
65%
clopidogrel
prasugrel

Baseline Characteristics:

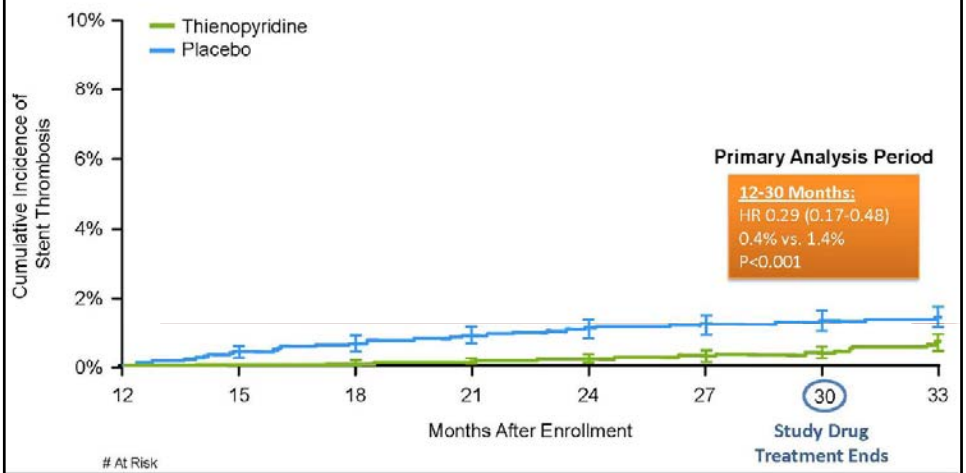
Table 1. Characteristics of Patients Who Were Treated with Drug-Eluting Stents and Who Underwent Randomization.*

Characteristic	Continued Thienopyridine (N=5020)	Placebo (N=4941)
Patients		
Age — yr	61.8±10.2	61.6±10.1
Female sex — no. (%)	1242 (24.7)	1284 (26.0)
Nonwhite race — no./total no. (%)†	438/4918 (8.9)	419/4847 (8.6)
Hispanic or Latino ethnic group — no./total no. (%)†	159/4924 (3.2)	159/4847 (3.3)
Weight — kg†	91.5±19.7	91.5±19.4
Body-mass index§	30.5±5.8	30.6±5.8
Diabetes mellitus — no./total no. (%)	1556/5006 (31.1)	1481/4927 (30.1)
Hypertension — no./total no. (%)	3796/5006 (75.8)	3649/4934 (74.0)
Current cigarette smoker or within past year — no./total no. (%)	1222/4965 (24.6)	1210/4893 (24.7)
Stroke or TIA — no./total no. (%)	155/5006 (3.1)	169/4931 (3.4)
Congestive heart failure — no./total no. (%)	238/5001 (4.8)	223/4926 (4.5)
Peripheral arterial disease — no./total no. (%)	284/4937 (5.8)	284/4857 (5.8)
Prior PCI — no./total no. (%)	1518/4995 (30.4)	1529/4928 (31.0)
Prior CABG — no./total no. (%)	568/5012 (11.3)	581/4930 (11.8)
Prior myocardial infarction — no./total no. (%)	1092/4953 (22.0)	1026/4870 (21.1)
Indication for PCI — no. (%)		
STEMI	534 (10.6)	511 (10.3)
NSTEMI	776 (15.5)	767 (15.5)
Unstable angina¶	838 (16.7)	825 (16.7)
Stable angina	1882 (37.5)	1870 (37.8)
Other	990 (19.7)	968 (19.6)
Any risk factor for stent thrombosis — no./total no. (%)‖	2410/4751 (50.7)	2389/4685 (51.0)

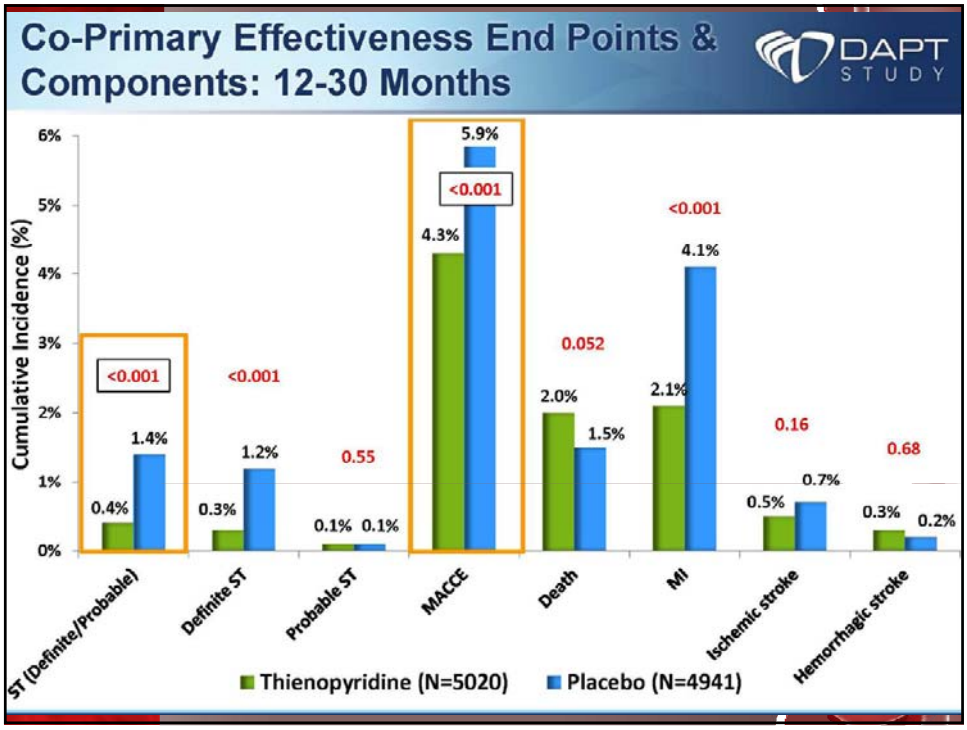
Mauri et al. NEJM. 2014. 371(23): 2155-66

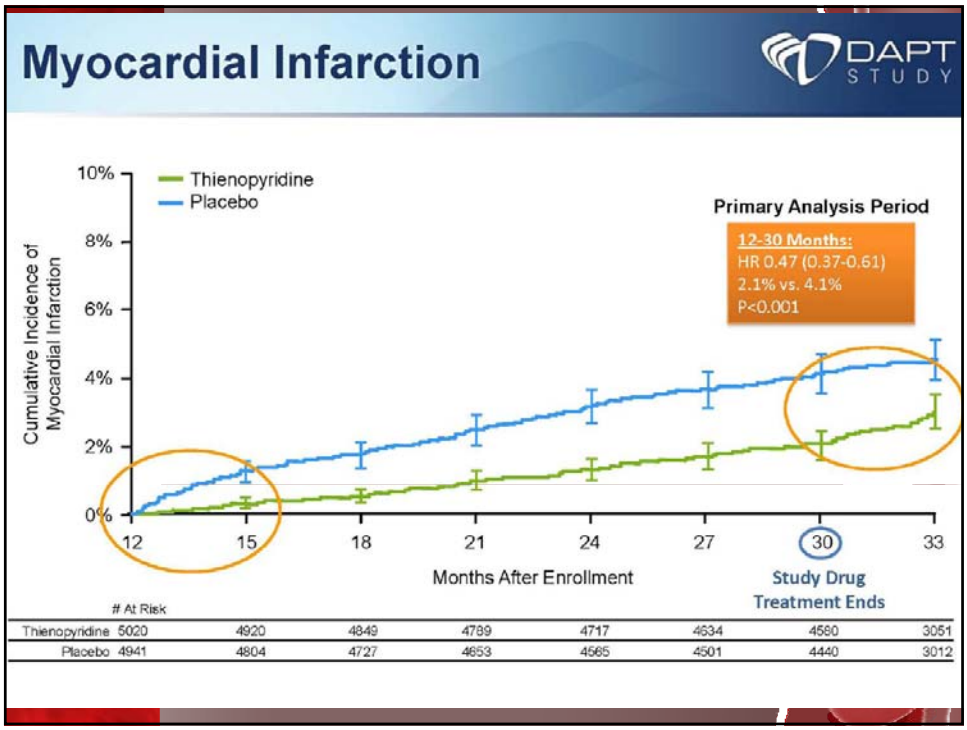
Co-Primary Effectiveness End Point Stent Thrombosis

DAPT STUDY



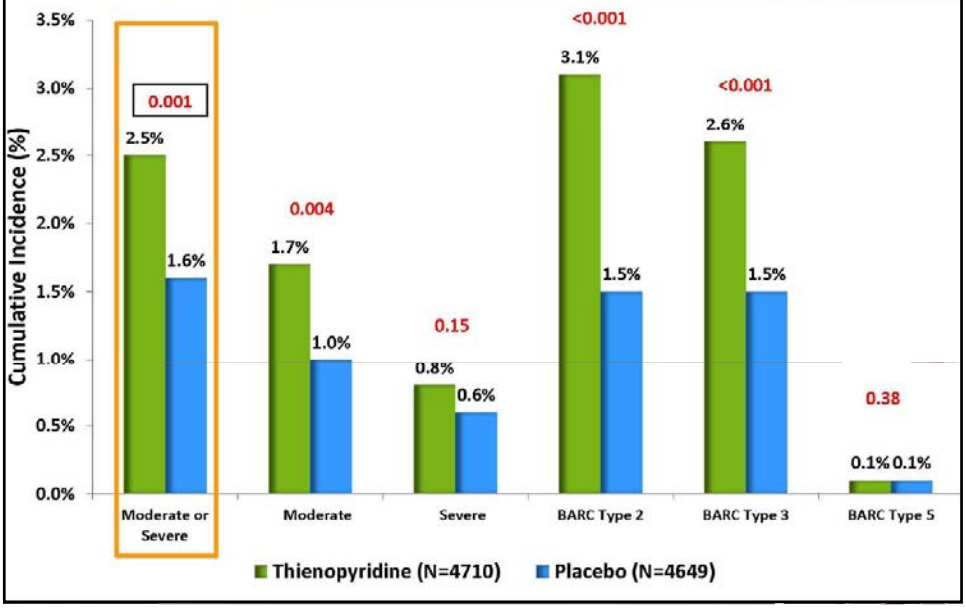
# At Risk							
Thienopyridine 5020	4934	4870	4828	4765	4686	4642	3110
Placebo 4941	4845	4775	4721	4651	4603	4556	3105


Co-Primary Effectiveness End Points & Components: 12-30 Months
DAPT STUDY
Cumulative Incidence (%)
6%
5%
4%
3%
2%
1%
0%
<0.001
1.4%
0.4%
<0.001
1.2%
0.3%
0.55
0.1%
0.1%
5.9%
<0.001
4.3%
0.052
2.0%
1.5%
<0.001
4.1%
2.1%
0.16
0.7%
0.5%
0.68
0.3%
0.2%
ST (Definite/Probable)
Definite ST
Probable ST
MACCE
Death
MI
Ischemic stroke
Hemorrhagic stroke
Thienopyridine (N=5020)
Placebo (N=4941)


Myocardial Infarction
DAPT STUDY
Thienopyridine
Placebo
Primary Analysis Period
12-30 Months:
HR 0.47 (0.37-0.61)
2.1% vs. 4.1%
P<0.001
Cumulative Incidence of Myocardial Infarction
10%
8%
6%
4%
2%
0%
12
15
18
21
24
27
30
33
Months After Enrollment
Study Drug Treatment Ends
At Risk
Thienopyridine 5020 4920 4849 4789 4717 4634 4580 3051
Placebo 4941 4804 4727 4653 4565 4501 4440 3012

Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months

DAPT STUDY



PEGASUS-TIMI 54: Study Design

Patients aged ≥50 years with a history of spontaneous MI 1–3 years prior to enrolment
AND at least one additional atherothrombosis risk factor*
(N=21,162)

- Ticagrelor 90 mg bid + ASA 75–150 mg/day
- Ticagrelor 60 mg bid + ASA 75–150 mg/day
- Placebo + ASA 75–150 mg/day

Minimum of 12 months' follow up:
Every 4 months in Year 1,
then semi-annually

Primary efficacy endpoint: CV death, MI or stroke
Primary safety endpoint: TIMI-defined major bleeding

*Age ≥65 years, diabetes mellitus, second prior MI, multivessel CAD or chronic non-end stage renal disease
bid, twice daily; CAD, coronary artery disease; TIMI, Thrombolysis in Myocardial Infarction

Bonaca MP *et al. Am Heart J* 2014;167-437–444
Bonaca MP *et al. N Engl J Med* 2015 [Epub ahead of print]

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Key Inclusion & Exclusion Criteria

PEGASUS TIMI 54

TIMI

KEY INCLUSION

- Age ≥50 years
- At least 1 of the following:
  - Age ≥65 years
  - Diabetes requiring medication
  - 2nd prior MI (>1 year ago)
  - Multivessel CAD
  - CrCl <60 mL/min
- Tolerating ASA and able to be dosed at 75-150 mg/d

KEY EXCLUSION

- Planned use of $P2Y_{12}$ antagonist, dipyridamole, cilostazol, or anticoag
- Bleeding disorder
- History of ischemic stroke, ICH, CNS tumor or vascular abnormality
- Recent GI bleed or major surgery
- At risk for bradycardia
- Dialysis or severe liver disease

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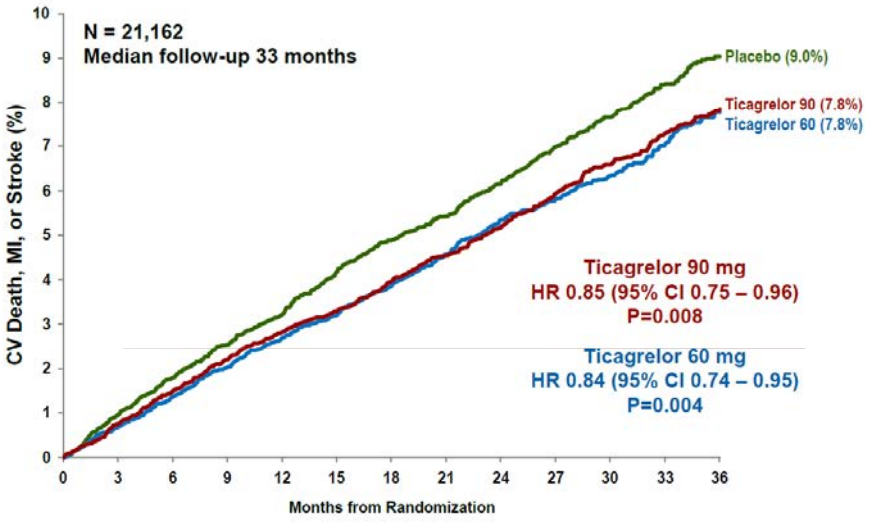
Bonaca MP et al. *Am Heart J* 2014;167:437-44

Primary Endpoint

PEGASUS TIMI 54

TIMI



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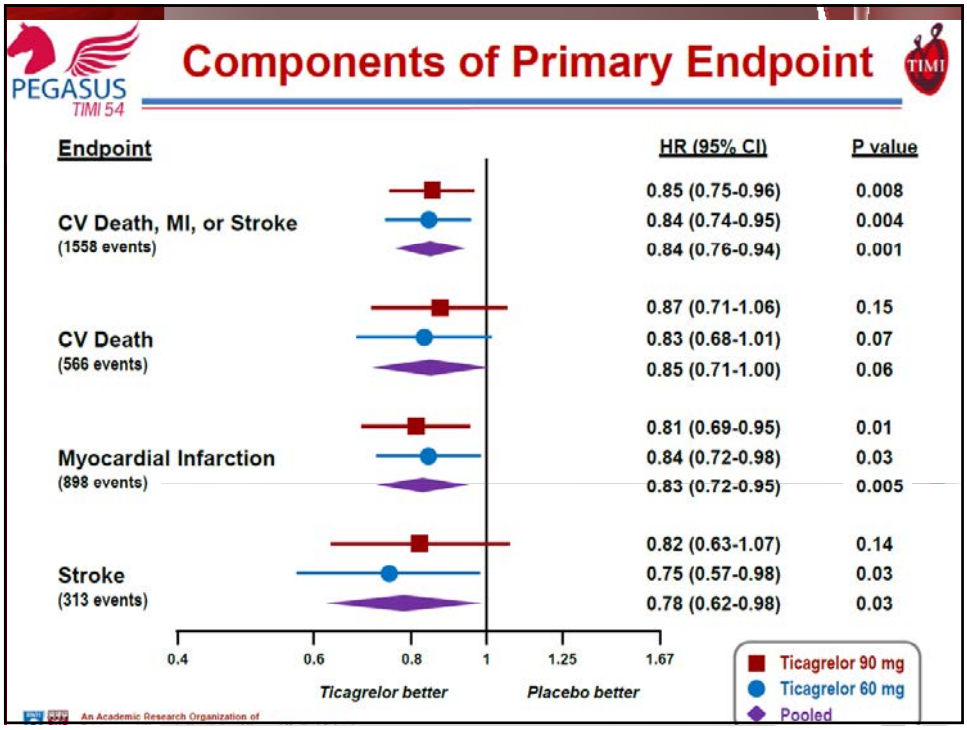
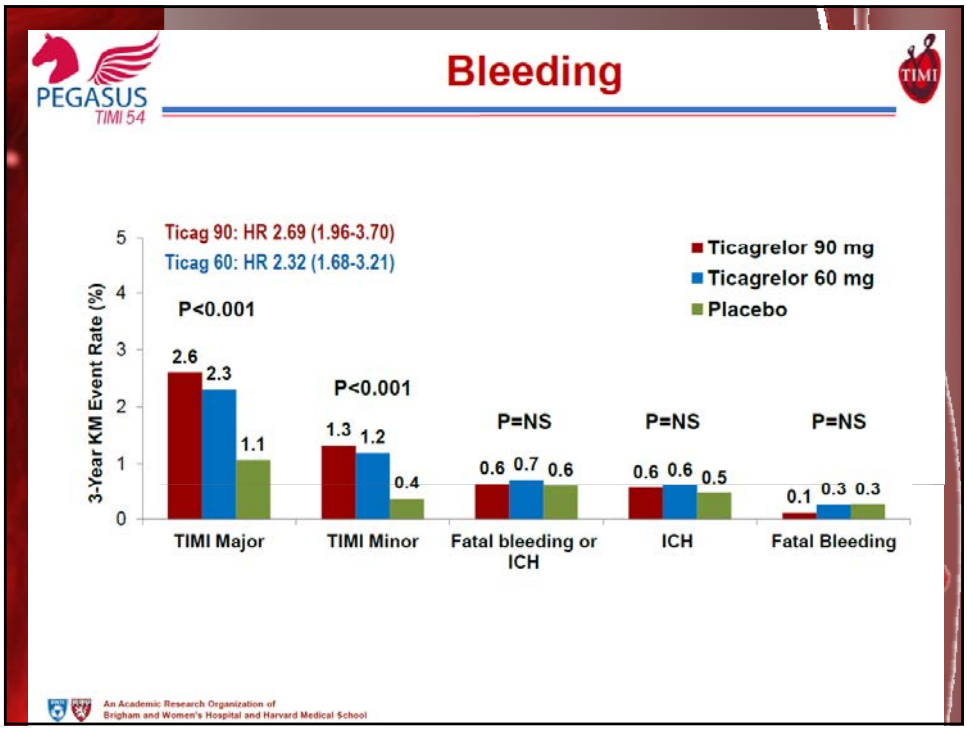

PEGASUS TIMI 54
Components of Primary Endpoint
TIMI
Endpoint
HR (95% CI)
P value
CV Death, MI, or Stroke
(1558 events)
0.85 (0.75-0.96)
0.84 (0.74-0.95)
0.84 (0.76-0.94)
0.008
0.004
0.001
CV Death
(566 events)
0.87 (0.71-1.06)
0.83 (0.68-1.01)
0.85 (0.71-1.00)
0.15
0.07
0.06
Myocardial Infarction
(898 events)
0.81 (0.69-0.95)
0.84 (0.72-0.98)
0.83 (0.72-0.95)
0.01
0.03
0.005
Stroke
(313 events)
0.82 (0.63-1.07)
0.75 (0.57-0.98)
0.78 (0.62-0.98)
0.14
0.03
0.03
0.4
0.6
0.8
1
1.25
1.67
Ticagrelor better
Placebo better
Ticagrelor 90 mg
Ticagrelor 60 mg
Pooled
An Academic Research Organization of


PEGASUS TIMI 54
Bleeding
TIMI
Ticag 90: HR 2.69 (1.96-3.70)
Ticag 60: HR 2.32 (1.68-3.21)
Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo
3-Year KM Event Rate (%)
0
1
2
3
4
5
P<0.001
2.6
2.3
1.1
P<0.001
1.3
1.2
0.4
P=NS
0.6
0.7
0.6
P=NS
0.6
0.6
0.5
P=NS
0.1
0.3
0.3
TIMI Major
TIMI Minor
Fatal bleeding or ICH
ICH
Fatal Bleeding
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Other Adverse Events

Adverse Event	Ticagrelor 90 mg bid (N=6988)	Ticagrelor 60 mg bid (N=6958)	Placebo (N=6996)	Ticagrelor 90 vs Placebo p-value	Ticagrelor 60 vs Placebo p-value
	3-yr KM rate (%)				
Dyspnea AE	18.9	15.8	6.4	P<0.001	P<0.001
Leading to study drug d/c	6.5	4.6	0.8	P<0.001	P<0.001
Severe	1.2	0.6	0.2	P<0.001	P<0.001
Bradyarrhythmia	2.0	2.3	2.0	P=0.31	P=0.10
Gout	2.3	2.0	1.5	P<0.001	P=0.01

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Duration of DAPT in Patients with Stable CAD Post PCI

COR	LOE	Recommendations
I	A	In patients with SIHD treated with DAPT after BMS implantation, $P2Y_{12}$ inhibitor therapy with clopidogrel should be given for a minimum of 1 month (94,95).
I	B-R [SR]	In patients with SIHD treated with DAPT after DES implantation, $P2Y_{12}$ inhibitor therapy with clopidogrel should be given for at least 6 months (17,18,21,30,96,97).

Levine et al. JACC. 2016. *In Press*

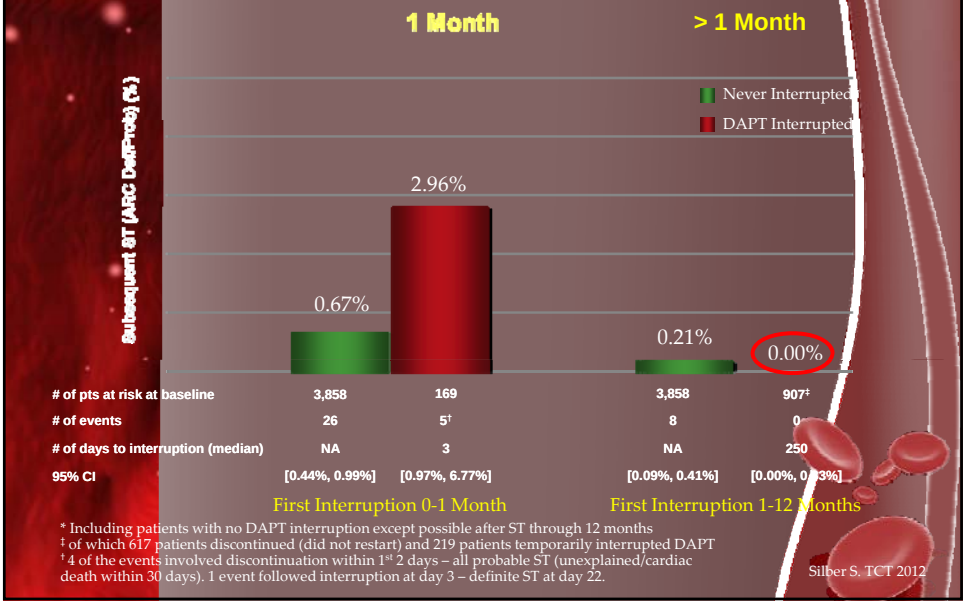
Duration of DAPT in Patients with Stable CAD Post PCI

IIb	C-LD	In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 3 months may be reasonable (19,20,34,36,37).

Levine et al. JACC. 2016. *In Press*

RESOLUTE Pooled DAPT Interruption Analysis

Timing of First DAPT Interruption and ST Through 1 Year

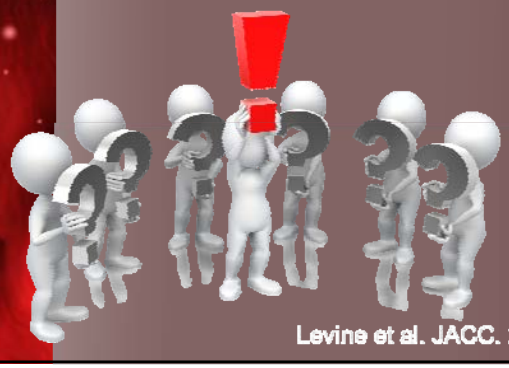


* Including patients with no DAPT interruption except possible after ST through 12 months
‡ of which 617 patients discontinued (did not restart) and 219 patients temporarily interrupted DAPT
† 4 of the events involved discontinuation within 1st 2 days – all probable ST (unexplained/cardiac death within 30 days). 1 event followed interruption at day 3 – definite ST at day 22.

Silber S. TCT 2012

Duration of DAPT in Patients with Stable CAD Post PCI

IIb	A [SR]	In patients with SIHD treated with DAPT after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable (16,22,24-26,30,50).



Levine et al. JACC. 2016. *In Press*

The Rationale for Shorter Duration…

Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials

Tullio Palmerini, Umberto Benedetto, Letizia Bacchi-Reggiani, Diego Della Riva, Giuseppe Biondi-Zoccai, Fausto Feres, Alexandre Abizaid, Myeong-Ki Hong, Byeong-Keuk Kim, Yangsoo Jang, Hyo-Soo Kim, Kyung Woo Park, Philippe Genereux, Deepak L. Bhatt, Carlotta Orlandi, Stefano De Servi, Mario Petrou, Claudio Rapezzi, Gregg W Stone

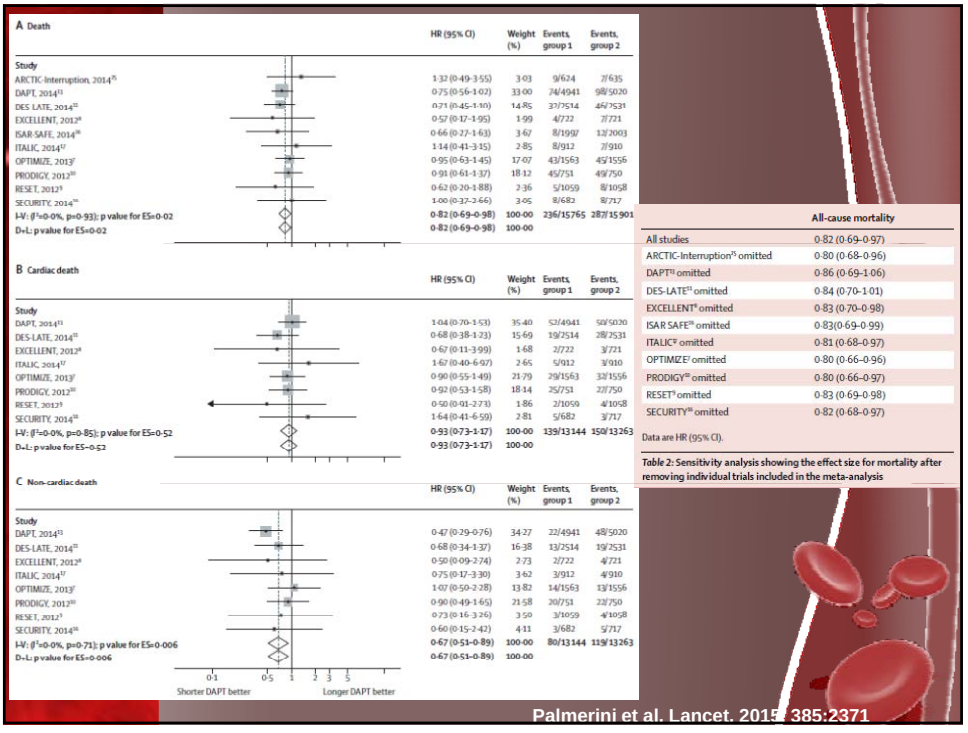
Palmerini et al. Lancet. 2015. 385:2371

10 trials with 31 666 patients DAPT duration after DES

	Number of patients in each treatment group	Primary endpoint	Design and randomisation	Follow-up duration after randomisation	Results of the primary endpoint
ARCTIC-Interruption, 2014[25]	12 months (n=624); 18–24 months (n=635)	Death, myocardial infarction, stent thrombosis, cerebrovascular accident, or target vessel revascularisation	Superiority, randomisation at discontinuation of dual antiplatelet therapy	Median of 17 months	Superiority of >12-month dual antiplatelet therapy not shown
DAPT, 2014[13]	12 months (n=4941); 30 months (n=5020)	Death, myocardial infarction, stent thrombosis, cerebrovascular accident, or bleeding	Superiority, randomisation at discontinuation of dual antiplatelet therapy	18 months	Superiority of 30-month dual antiplatelet therapy shown
DES-LATE, 2013[23]	12 months (n=2514); 36 months (n=2531)	Cardiac death, myocardial infarction, or cerebrovascular accident	Superiority, randomisation at discontinuation of dual antiplatelet therapy	24 months	Superiority of 24-month dual antiplatelet therapy not shown
EXCELLENT, 2012[24]	6 months (n=722); 12 months (n=721)	Cardiac death, myocardial infarction, and ischaemia-driven target vessel revascularisation	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
ISAR-SAFE, 2014[26]	6 months (n=1997); 12 months (n=2003)	Death, myocardial infarction, stent thrombosis, cerebrovascular accident, or bleeding	Non-inferiority, randomisation at discontinuation of dual antiplatelet therapy	9 months	Non-inferiority shown
ITALIC, 2014[27]	6 months (n=952); 24 months (n=941)	Death, myocardial infarction cerebrovascular accident, target vessel revascularisation, or bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
OPTIMIZE, 2013[7]	3 months (n=1563); 12 months (n=1556)	Death, myocardial infarction, cerebrovascular accident, or major bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
PRODIGY, 2012[28]	6 months (n=751); 24 months (n=750)	Death, myocardial infarction, or cerebrovascular accident	Superiority, randomisation 1 month after percutaneous coronary intervention	24 months	Superiority of 24-month dual antiplatelet therapy not shown
RESET, 2012[8]	3 months (n=1059); 12 months (n=1058)	Cardiac death, myocardial infarction, stent thrombosis, target vessel revascularisation, or major bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
SECURITY, 2014[29]	6 months (n=682); 12 months (n=717)	Cardiac death, myocardial infarction cerebrovascular accident, stent thrombosis, bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown

Table 1: Main characteristics of the randomised trials included in the meta-analysis

Palmerini et al. Lancet. 2015. 385:2371

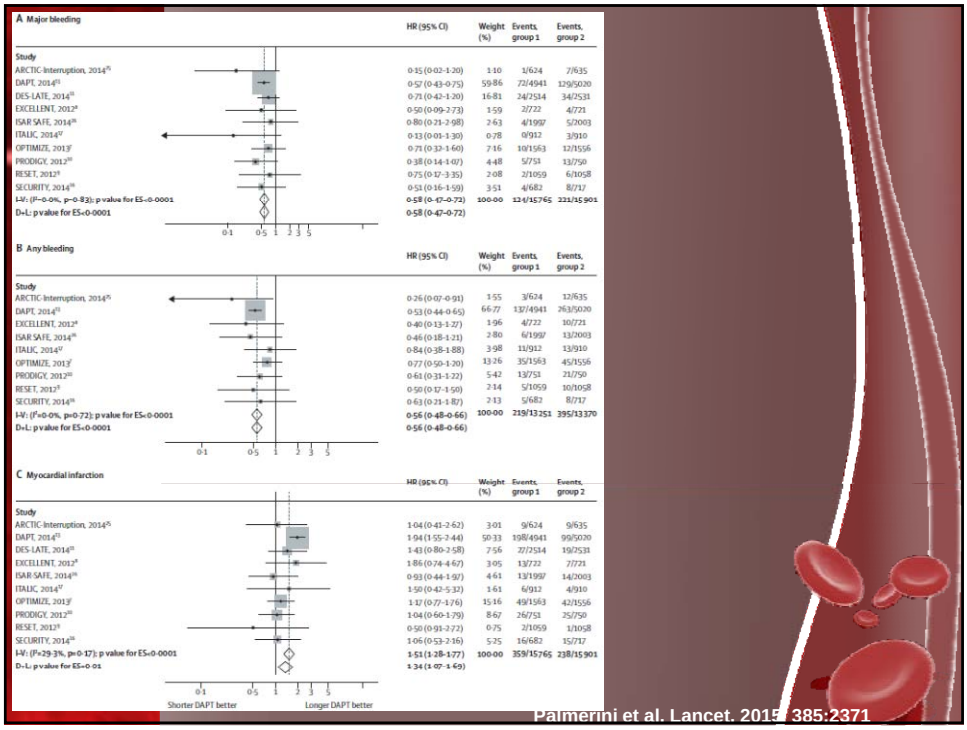


All-cause mortality	
All studies	0·82 (0·69–0·97)
ARCTIC-Interruption[25] omitted	0·80 (0·68–0·96)
DAPT[13] omitted	0·86 (0·69–1·06)
DES-LATE[23] omitted	0·84 (0·70–1·01)
EXCELLENT[24] omitted	0·83 (0·70–0·98)
ISAR SAFE[26] omitted	0·83 (0·69–0·99)
ITALIC[27] omitted	0·81 (0·68–0·97)
OPTIMIZE[7] omitted	0·80 (0·66–0·96)
PRODIGY[28] omitted	0·80 (0·66–0·97)
RESET[8] omitted	0·83 (0·69–0·98)
SECURITY[29] omitted	0·82 (0·68–0·97)

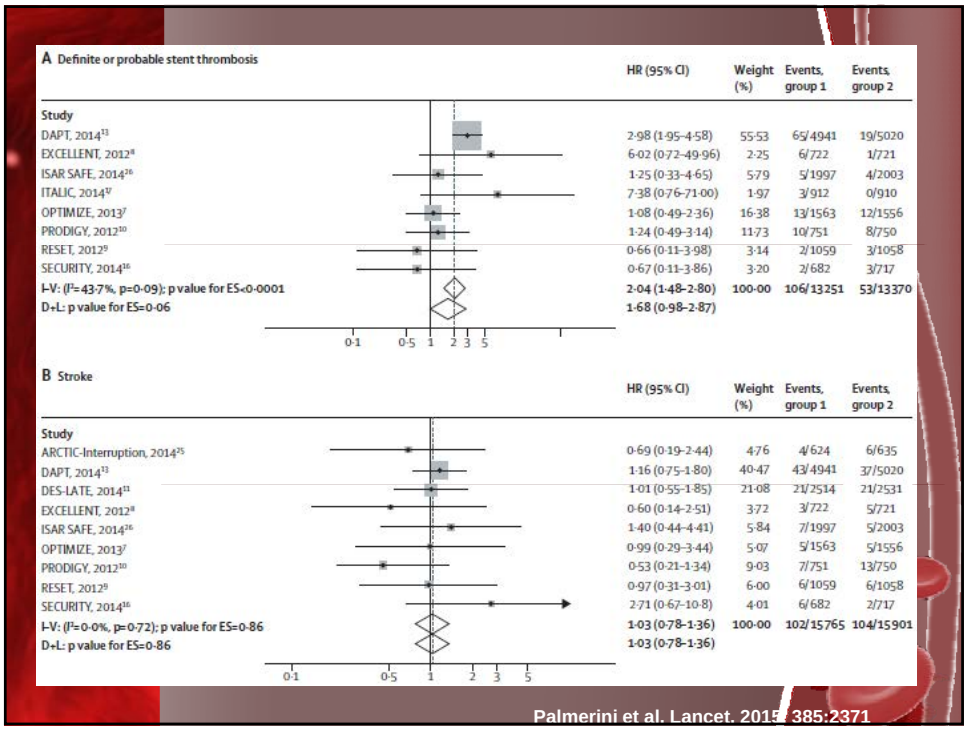
Data are HR (95% CI).

Table 2: Sensitivity analysis showing the effect size for mortality after removing individual trials included in the meta-analysis

Palmerini et al. Lancet. 2015. 385:2371



Palmerini et al. Lancet. 2015; 385:2371



Palmerini et al. Lancet. 2015; 385:2371

	≤6-month *vs* 1-year DAPT	≤6-month *vs* >1-year DAPT	1-year *vs* >1-year DAPT
All-cause death	0·95 (0·76–1·20)	0·78 (0·59–1·00)	0·82 (0·65–1·00)
Cardiac death	0·96 (0·68–1·40)	0·90 (0·62–1·30)	0·93 (0·69–1·20)
Non-cardiac death	1·00 (0·69–1·60)	0·65 (0·41–1·00)	0·61 (0·42–0·87)
Myocardial infarction	1·00 (0·75–1·30)	1·70 (1·30–2·40)	1·70 (1·40–2·10)
Definite or probable stent thrombosis	1·10 (0·66–1·70)	2·70 (1·50–5·00)	2·50 (1·70–4·00)
Major bleeding	0·59 (0·36–0·95)	0·34 (0·20–0·55)	0·58 (0·45–0·74)

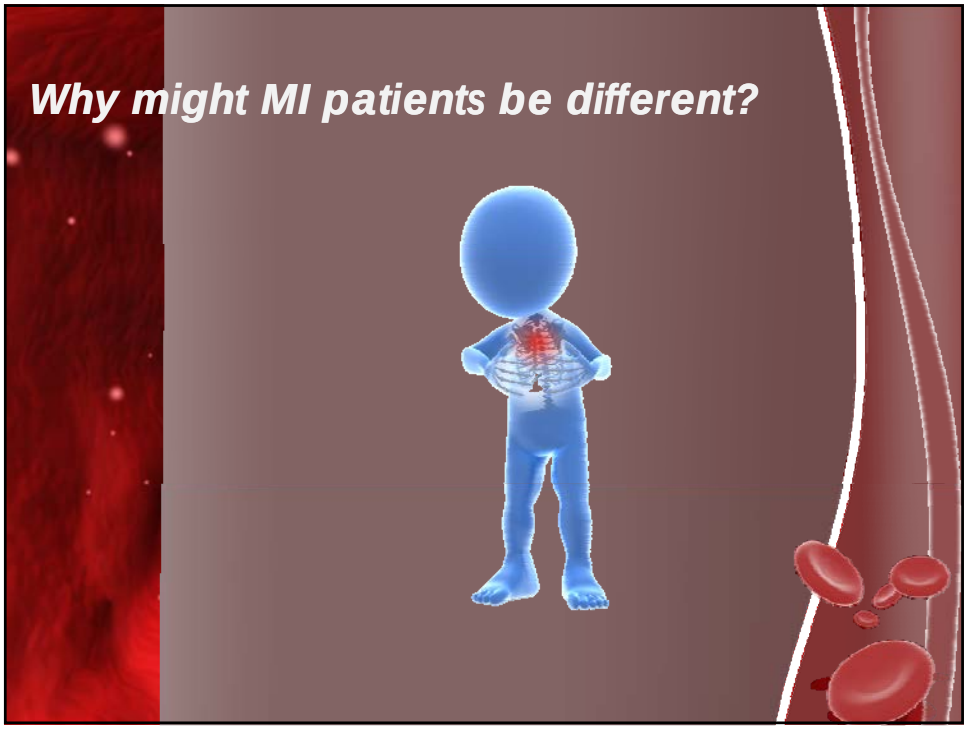
Data are HR (95% CrI). DAPT=dual antiplatelet therapy. HR=hazard ratio. CrI=credible intervals.

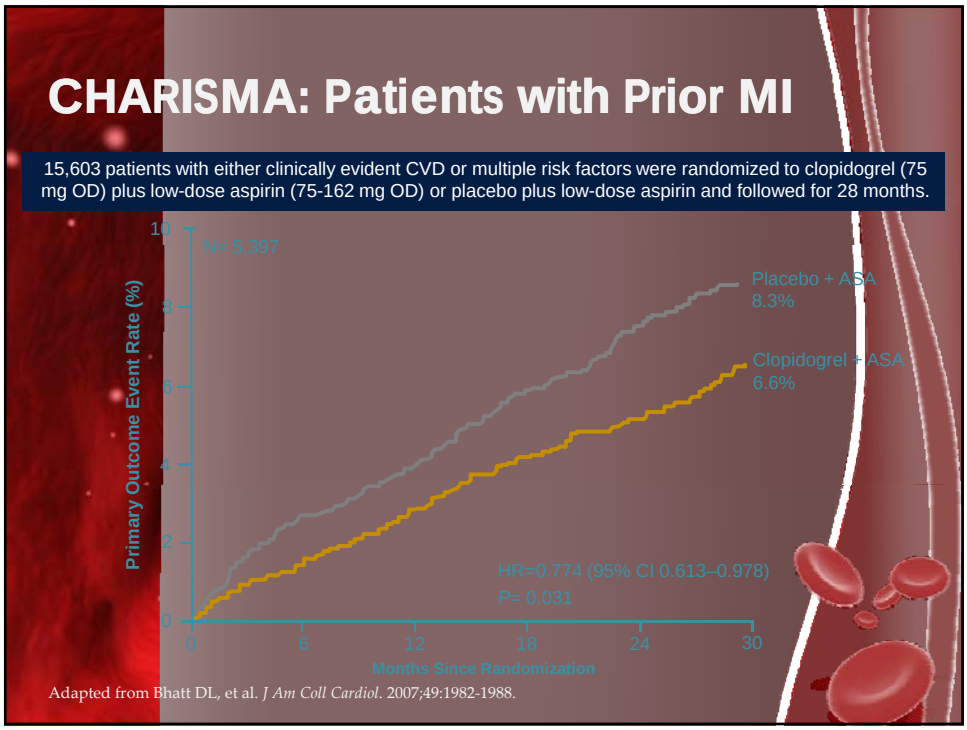
Table 3: **Clinical outcomes stratified by different durations of dual antiplatelet therapy established by network meta-analysis**

Palmerini et al. Lancet. 2016. 385:2371

Adding up the results…

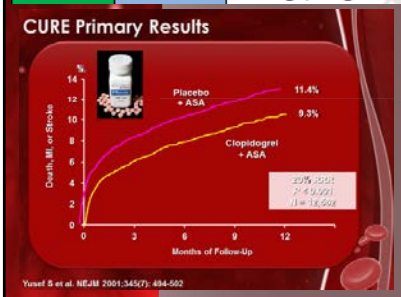
- Extended DAPT was associated with 22% increase in all cause mortality
- This is primarily due to 49% increase in non-cardiac mortality and NO significant differences in cardiac mortality
- Significantly, extended DAPT comes with a cost of increase bleeding


Why might MI patients be different?


CHARISMA: Patients with Prior MI
15,603 patients with either clinically evident CVD or multiple risk factors were randomized to clopidogrel (75 mg OD) plus low-dose aspirin (75-162 mg OD) or placebo plus low-dose aspirin and followed for 28 months.
Primary Outcome Event Rate (%)
10
8
6
4
2
0
N= 5,397
Placebo + ASA
8.3%
Clopidogrel + ASA
6.6%
HR=0.774 (95% CI 0.613–0.978)
P= 0.031
0
6
12
18
24
30
Months Since Randomization
Adapted from Bhatt DL, et al. J Am Coll Cardiol. 2007;49:1982-1988.

Duration of DAPT in Patients with ACS Post PCI

COR	LOE	Recommendations
I	B-R	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after BMS or DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months (16,50-55,72,96-98).
I	B-NR	In patients treated with DAPT, the recommended daily dose of aspirin is 81 mg (range, 75 mg to 100 mg) (56-60,75-78).



Levine et al. JACC. 2016. *In Press*

Yusef et al. NEJM. 2001; 345(7):494-502

Duration of DAPT in Patients with ACS Post PCI

IIb	A [SR]	In patients with ACS (NSTE-ACS or STEMI) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable (16,22-26,28,30,40,41,43,53,54,72).

Levine et al. JACC. 2016. *In Press*

Duration of DAPT in Patients with ACS Post PCI

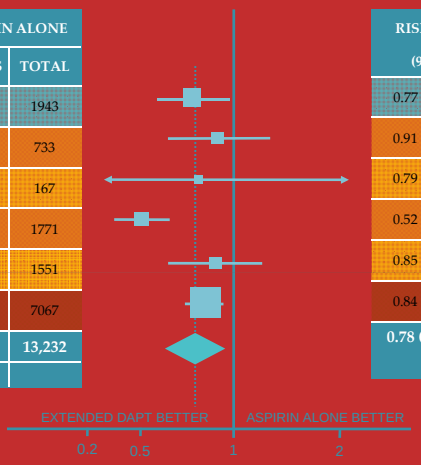
IIb	C-LD	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable (17-21,34,36,37).

Levine et al. JACC. 2016. *In Press*

Primary Endpoint: CV Death, MI, or Stroke

33,435 patients followed over a mean 31 months as part of a collaborative meta-analysis of CV events in patients with previous MI treated with DAPT with aspirin alone for > 1 year

STUDY	EXTENDED DAPT		ASPIRIN ALONE		RISK RATIO (95% CI)
	EVENTS	TOTAL	EVENTS	TOTAL	
CHARISMA	125	1,903	162	1943	0.77 (0.61,0.98)
PRODIGY	63	732	69	733	0.91 (0.65-1.28)
ARCTIC-Interruption	3	156	4	167	0.79 (0.18-3.51)
DAPT	59	1,805	108	1771	0.52 (0.38-0.72)
DES LATE	56	1,512	66	1551	0.85 (0.60-1.21)
PEGASUS-TIMI 54	980	14,095	578	7067	0.84 (0.76-0.94)
TOTAL	1,286	20,203	987	13,232	0.78 (0.67-0.90)
	6.4%		7.5%		



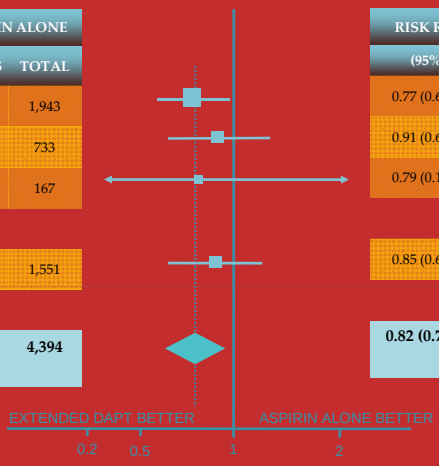
P = 0.001

CI: confidence interval; DAPT: dual antiplatelet therapy; RR: risk ratio.
Udell JA, *et al. Eur Heart J.* 2015 Aug 31. Available at eurheartj.oxfordjournals.org.

Primary Endpoint – Removed PEGASUS-TIMI 54 & DAPT

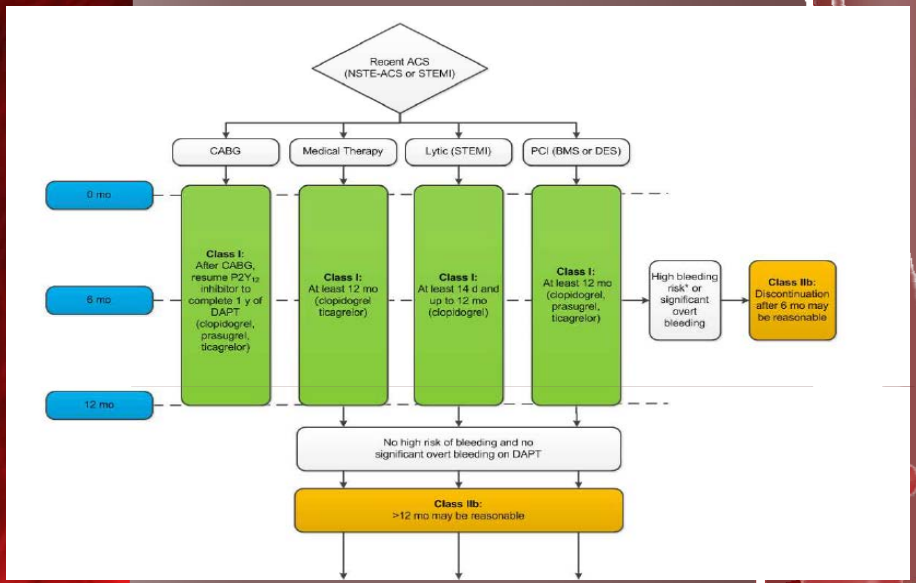
	EXTENDED DAPT		ASPIRIN ALONE		RISK RATIO
STUDY	EVENTS	TOTAL	EVENTS	TOTAL	(95% CI)
CHARISMA	125	1,903	162	1,943	0.77 (0.61-0.98)
PRODIGY	63	732	69	733	0.91 (0.65-1.28)
ARCTIC-Interruption	3	156	4	167	0.79 (0.18-3.51)
DES LATE	56	1,512	66	1,551	0.85 (0.60-1.21)
TOTAL	**247**	**4,303**	**301**	**4,394**	**0.82 (0.70-0.97)**
	5.7%		**6.9%**		

P = 0.02



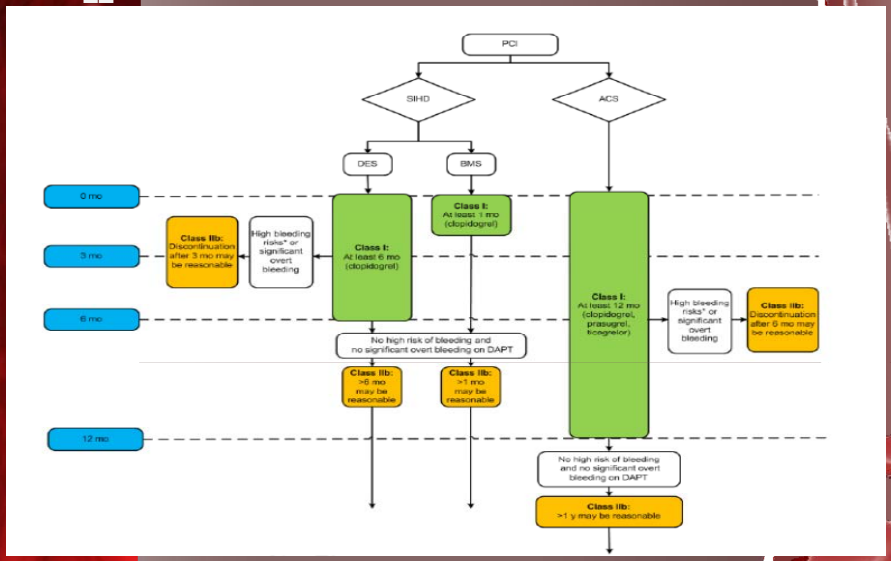
Udell JA, et al. *Eur Heart J.* 2015 Aug 31. Available at eurheartj.oxfordjournals.org.

Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor in Patients after ACS



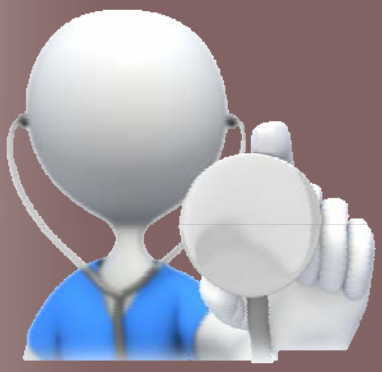
Levine et al. JACC. 2016. *In Press*

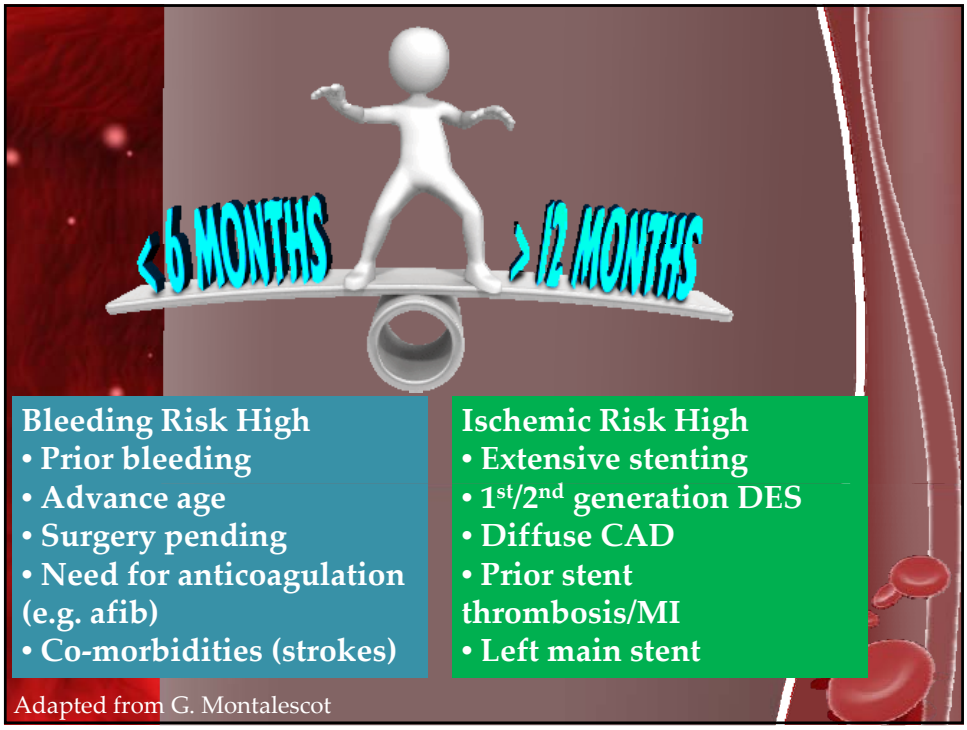
Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor in Patients after PCI



Levine et al. JACC. 2016. *In Press*

How to Apply this to Clinical Practice?





Predictors of Net Treatment Effect

	Characteristics	Impact on Net Treatment Effect	% of Variation Explained
Bleeding Predictors	Age ≥ 75	-1.2%	6.0%
	Age 65 - < 75	-0.5%	2.1%
	Age < 65 (reference)	-	-
Ischemia Predictors	Prior PCI or MI	1.1%	14.6%
	Stent Diameter < 3 mm	0.9%	10.1%
	CHF or LVEF < 30%	1.9%	9.9%
	MI at Presentation	1.0%	9.6%
	Paclitaxel-Eluting Stent	1.0%	8.8%
	Cigarette Smoker	0.7%	4.3%
	Diabetes	0.6%	4.3%
	Vein Graft PCI	1.6%	3.7%
Bleeding and Ischemia Predictors	Hypertension	0.2%	0.4%
	Renal Insufficiency	0.4%	0.3%
	PAD	-0.1%	0.04%

Yeh et al. AHA 2015

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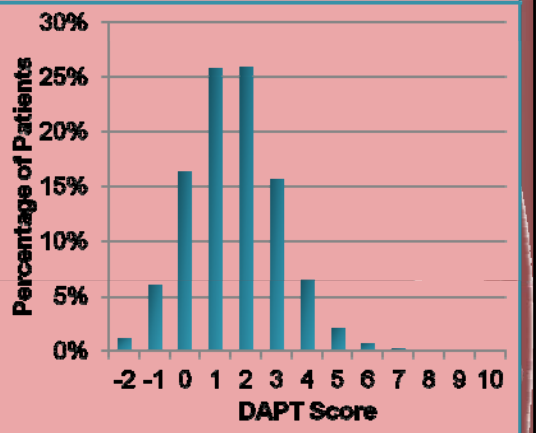
The DAPT Score

Variable	Points
Patient Characteristic	
Age	
≥ 75	-2
65 - <75	-1
< 65	0
Diabetes Mellitus	1
Current Cigarette Smoker	1
Prior PCI or Prior MI	1
CHF or LVEF < 30%	2
Index Procedure Characteristic	
MI at Presentation	1
Vein Graft PCI	2
Stent Diameter < 3mm	1

Distribution of DAPT Scores among all randomized subjects in the DAPT Study



Yeh et al. AHA 2015

The DAPT Score - Conclusions

Among patients who have not had a major ischemic or bleeding event within the first year after PCI:

The DAPT Score identified patients for whom ischemic benefits outweighed bleeding risks, and patients for whom bleeding risks outweighed ischemic benefits.

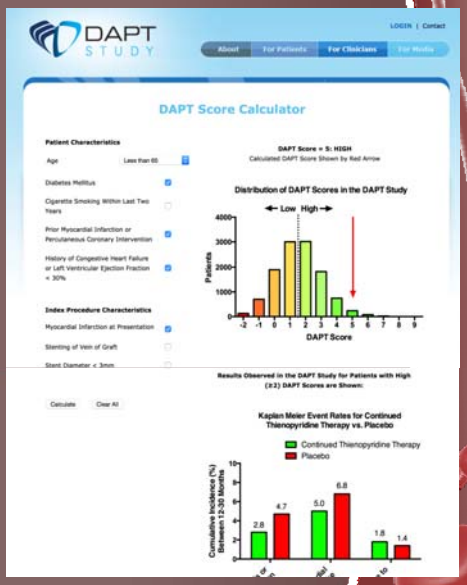
Low DAPT Score (< 2)
NNT to prevent ischemia = 153
NNH to cause bleeding = 64

High DAPT Score ≥ 2
NNT to prevent ischemia = 34
NNH to cause bleeding = 272

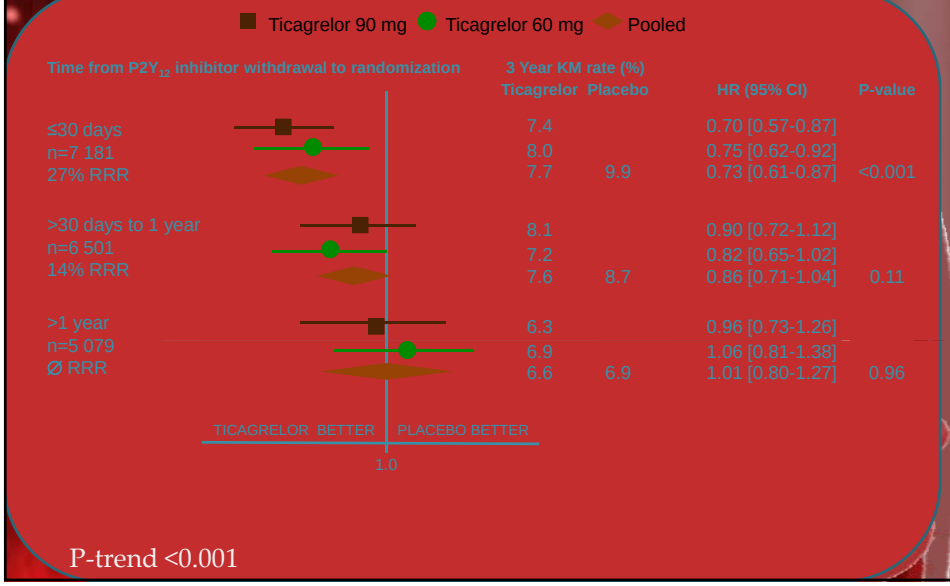
DAPT Score may help clinicians decide *who should, and who should not* be treated with extended DAPT

DAPT Score Calculator

DAPT Score calculator
www.daptstudy.org



Insights from PEGASUS-TIMI 54: CV Death/MI/Stroke in Relation to Time From P2Y12 Inhibitor Withdrawal



P-trend <0.001

Triple Therapy – The new frontier…

- The addition of DAPT to oral anticoagulant confers 2-3X increase in bleeding complications

Table 6. Summary and Synthesis of Guideline, Expert Consensus Documents, and Comprehensive Review Article Recommendations on the Management of Patients Treated With Triple Therapy (14,88,91-93)

- Assess ischemic and bleeding risks using validated risk predictors (e.g., CHA_2DS_2-VASc, HAS-BLED)
- Keep triple therapy duration as short as possible; dual therapy only (oral anticoagulant and clopidogrel) may be considered in select patients
- Consider a target INR of 2.0–2.5 when warfarin is used
- Clopidogrel is the $P2Y_{12}$ inhibitor of choice
- Use low-dose (≤100 mg daily) aspirin
- PPIs should be used in patients with a history of gastrointestinal bleeding and are reasonable to use in patients with increased risk of gastrointestinal bleeding

CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65-74 years, sex category; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly; INR, international normalized ratio; and PPIs, proton pump inhibitors.

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Perioperative Management of Non-cardiac Surgery in Patients on DAPT after PCI

COR	LOE	Recommendations
I	B-NR	Elective noncardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation (101-103,143-146).
I	C-EO	In patients treated with DAPT after coronary stent implantation who must undergo surgical procedures that mandate the discontinuation of $P2Y_{12}$ inhibitor therapy, it is recommended that aspirin be continued if possible and the $P2Y_{12}$ platelet receptor inhibitor be restarted as soon as possible after surgery.
IIa	C-EO	When noncardiac surgery is required in patients currently taking a $P2Y_{12}$ inhibitor, a consensus decision among treating clinicians as to the relative risks of surgery and discontinuation or continuation of antiplatelet therapy can be useful.
IIb	C-EO	Elective noncardiac surgery after DES implantation in patients for whom $P2Y_{12}$ inhibitor therapy will need to be discontinued may be considered after 3 months if the risk of further delay of surgery is greater than the expected risks of stent thrombosis.
III: Harm	B-NR	Elective noncardiac surgery should not be performed within 30 days after BMS implantation or within 3 months after DES implantation in patients in whom DAPT will need to be discontinued perioperatively (101-103,143-146).

The NEXT frontier ??…

In Summary…

- Updated guidelines suggest differentiating stable vs. ACS patients
- Shorter duration of therapy of up to 6 months for stable CAD post DES
- Minimum of 12 months for ACS patients after DES

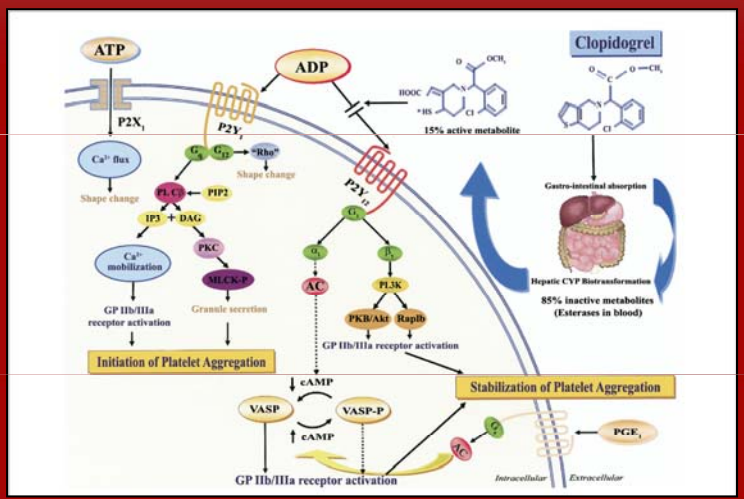
Summary (2)

For Long term DAPT… Ideal approach is to individualize care based on:

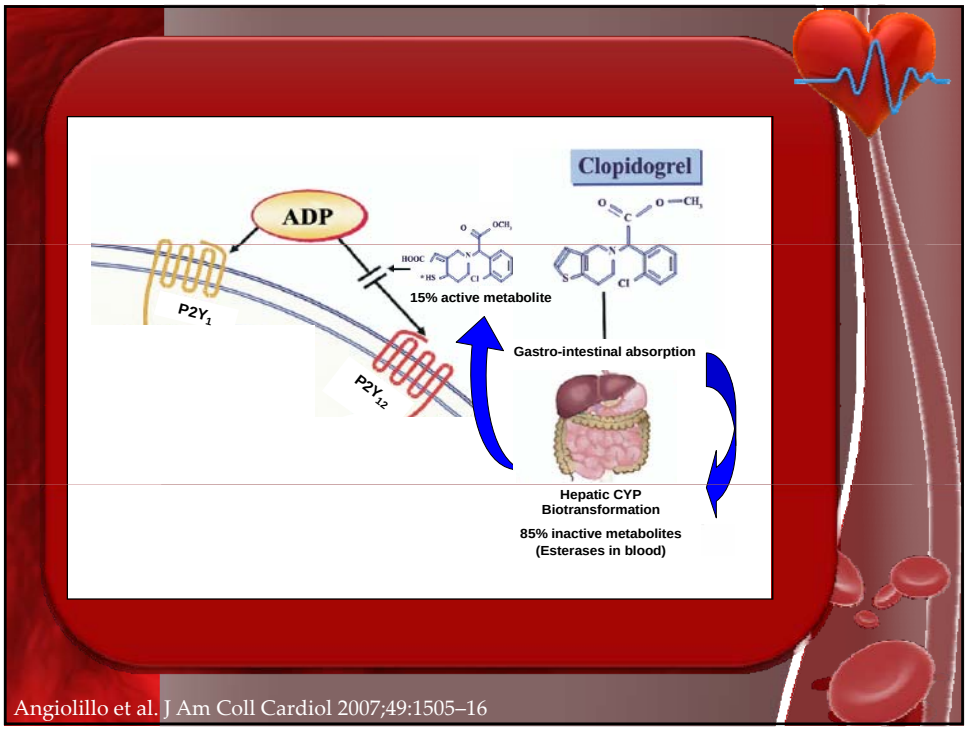
- Bleeding History
- Demographics
- Atherothrombotic Burden
- DAPT Score ?

Discuss with patients risk/benefits

When in doubt CALL us!



Angiolillo et al. J Am Coll Cardiol 2007;49:1505–16



Angiolillo et al. J Am Coll Cardiol 2007;49:1505–16

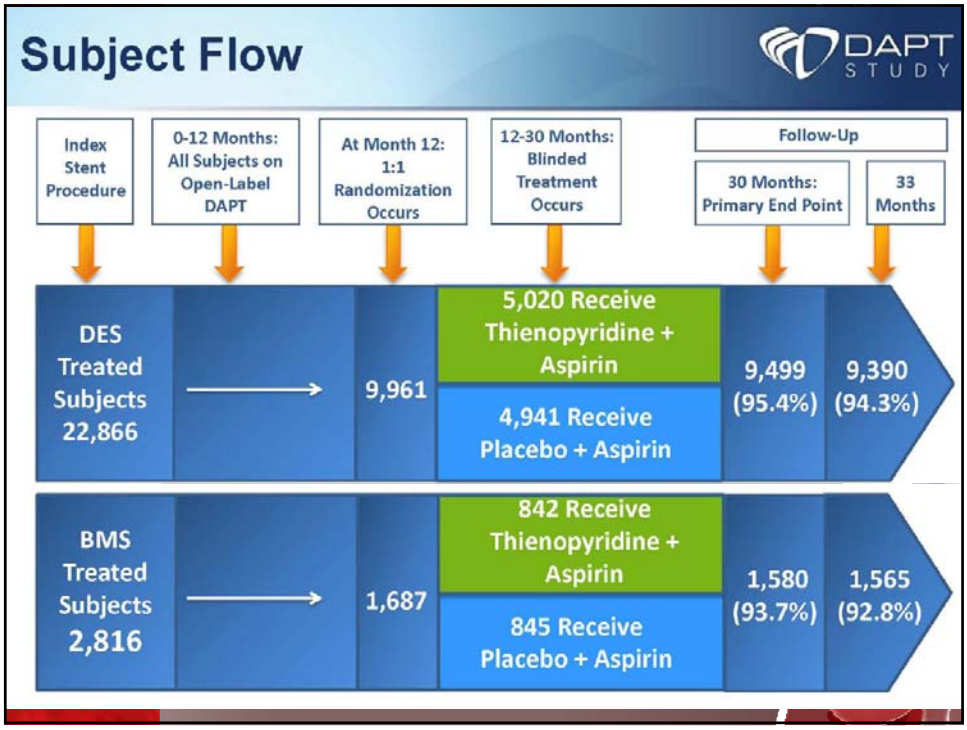
How were the duration guidelines designed…

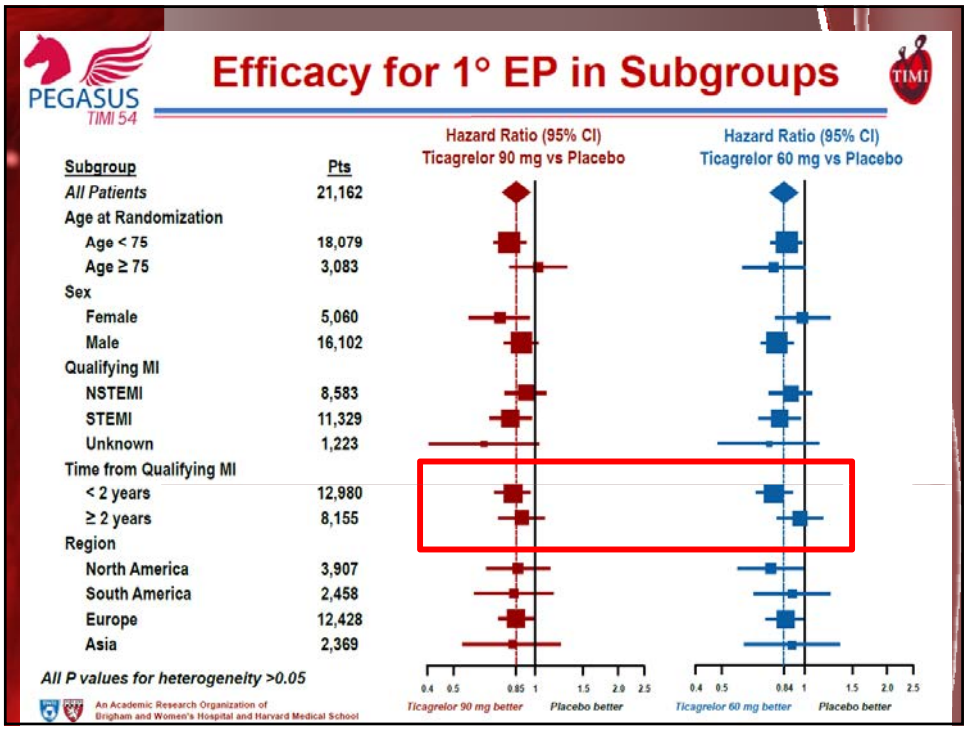
Table 2. Critical (PICOTS-Formatted) Questions on DAPT Duration

Q1: In patients treated with newer (non-first) generation DES for (1) SIHD or (2) ACS, compared with 12 months of DAPT, is 3–6 months of DAPT as effective in preventing stent thrombosis, preventing MACE and/or reducing bleeding complications?
Q2: In patients treated with newer (non-first) generation DES, compared with 12 months of DAPT, does >12 (18–48) months of DAPT result in differences in mortality rate, decreased MACE, decreased stent thrombosis, and/or increased bleeding?
Q3: In post-MI (NSTEMI or STEMI) patients who are clinically stable and >12 months past their event, does continued DAPT, compared with aspirin monotherapy, result in differences in mortality rate, decreased nonfatal MI, decreased MACE, and/or increased bleeding?

ACS indicates acute coronary syndrome; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; MACE, major adverse cardiac events; MI, myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; PICOTS, population, intervention, comparison, outcome, timing, and setting; SIHD, stable ischemic heart disease; and STEMI, ST-elevation myocardial infarction.

Levine et al. JACC. 2016. *In Press*


Subject Flow
DAPT STUDY
Index Stent Procedure
0-12 Months: All Subjects on Open-Label DAPT
At Month 12: 1:1 Randomization Occurs
12-30 Months: Blinded Treatment Occurs
Follow-Up
30 Months: Primary End Point
33 Months
DES Treated Subjects 22,866
9,961
5,020 Receive Thienopyridine + Aspirin
4,941 Receive Placebo + Aspirin
9,499 (95.4%)
9,390 (94.3%)
BMS Treated Subjects 2,816
1,687
842 Receive Thienopyridine + Aspirin
845 Receive Placebo + Aspirin
1,580 (93.7%)
1,565 (92.8%)

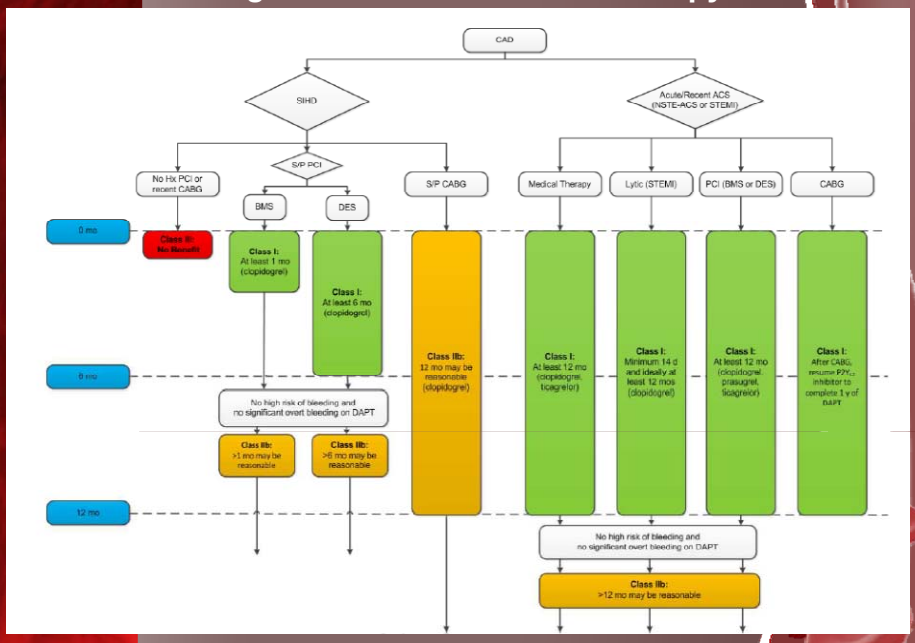

PEGASUS TIMI 54
Efficacy for 1° EP in Subgroups
TIMI
Hazard Ratio (95% CI) Ticagrelor 90 mg vs Placebo
Hazard Ratio (95% CI) Ticagrelor 60 mg vs Placebo
Subgroup
Pts
All Patients 21,162
Age at Randomization
Age < 75 18,079
Age ≥ 75 3,083
Sex
Female 5,060
Male 16,102
Qualifying MI
NSTEMI 8,583
STEMI 11,329
Unknown 1,223
Time from Qualifying MI
< 2 years 12,980
≥ 2 years 8,155
Region
North America 3,907
South America 2,458
Europe 12,428
Asia 2,369
All P values for heterogeneity >0.05
0.4 0.5 0.85 1 1.5 2.0 2.5
Ticagrelor 90 mg better
Placebo better
0.4 0.5 0.84 1 1.5 2.0 2.5
Ticagrelor 60 mg better
Placebo better
An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

Trials Evaluating Prolonged Dual Antiplatelet Therapy Following MI

Trial	Subgroup /Population	N	Drug	Duration (months)	MACE Events	Bleeding EP
CHARISMA[1]	Stable prior MI (mean 24 mo.)	3,846	Clopidogrel	28	287	GUSTO mod/severe
PRODIGY[2]	PCI for ACS	1,465	Clopidogrel	6 vs. 24	132	TIMI major
ARCTIC-Interruption[3]	PCI for ACS (excluded STEMI)	323	Clopidogrel or Prasugrel	12 vs. 24	7	STEEPLE major
DAPT[4]	PCI for MI subgroup	3,576	Clopidogrel or Prasugrel	12 vs. 30	167	GUSTO mod/severe
DES-LATE[5]	PCI for ACS	3,063	Clopidogrel	12 vs. 24	122	TIMI major
PEGASUS TIMI-54[6]	Stable prior MI (median 20 mo.)	21,162	Ticagrelor	33	1,558	TIMI major
Total		33,435		30	2,273	

1. Bhatt DL, *et al. J Am Coll Cardiol*. 2007;49:1982-1988; 2. Valgimigli M, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. *Circulation*. 2012;125(16):2015-26; 3. Collet JP, ARCTIC Iinvestigators. *Lancet*. 2014;384(9954):1577-85; 4. Mauri L, *et al*. DAPT Study Investigators. *N Engl J Med*. 2014;371(23):2155-66; 5. Lee CW, *et al*. *Circulation*. 2014;129(3):304-1; 6. Bonaca MP, *et al*. *N Engl J Med*. 2015;372:1791-800.

Master Algorithm on Duration of Therapy



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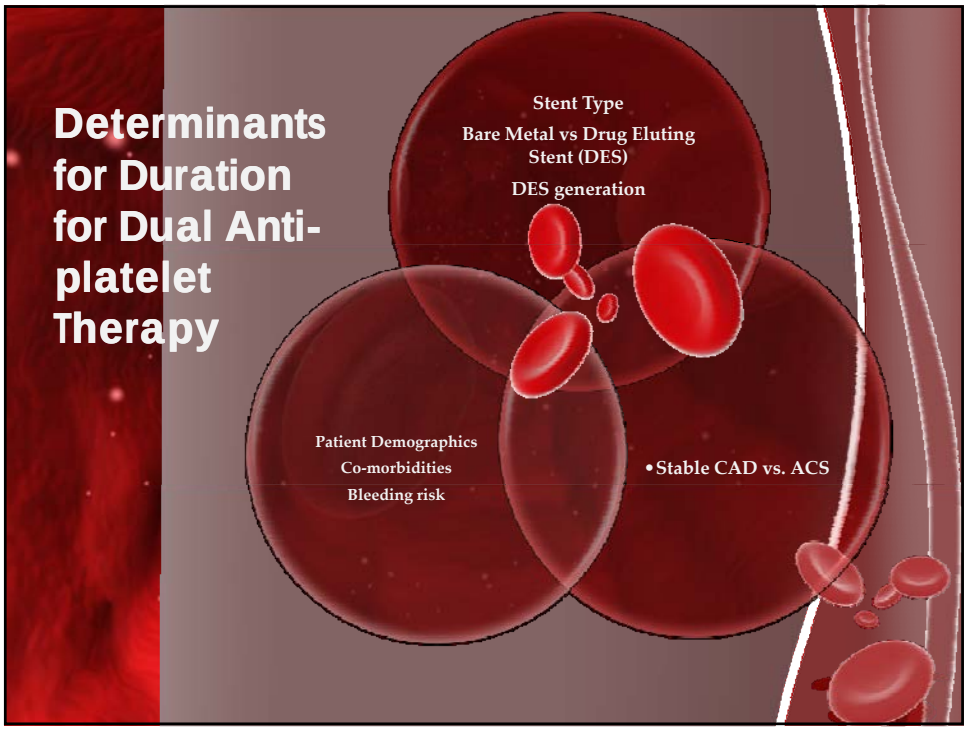
Determinants for Duration for Dual Anti-platelet Therapy
Stent Type
Bare Metal vs Drug Eluting Stent (DES)
DES generation
Patient Demographics
Co-morbidities
Bleeding risk
•Stable CAD vs. ACS