Optimal duration of DAPT in the era of new generation stents

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Contents

- Duration of DAPT on ACS
- Duration of DAPT on non-ACS with newer generation stent
- Meta-analysis for DAPT duration
- Tentative conclusion

So many considering points to decide …

- **Lesion specific vs patients specific**
  - bifurcation, left main, complex stenting, stent type
  - ACS, NIDDM, CKD, multiple CVD, atrial fibrillation

- **Bleeding**
  - high risk of bleeding population, chronic use of NSAIDs, OAC

- **Potency of drugs**
  - clopidogrel
  - Prasugrel
  - Ticagrelor

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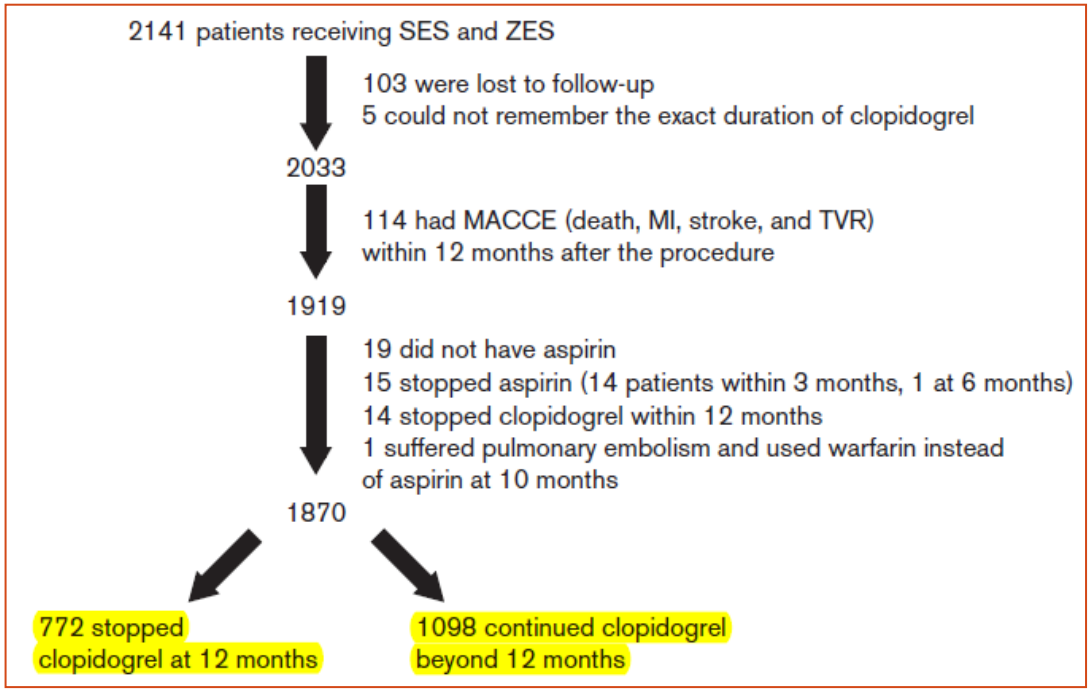
Longer vs shorter DAPT in Cypher Vs. Endeavor

- **1,870 patients receiving SES and ZES**
  - Randomized into 12 mo or beyond 12 mo DAPT duration



- **Follow up: 28.2±7.4 months**
- **Beyond 12 mo DAPT (n=1,098)**
  - 15%: 12-18 mo
  - 53%: 18-24 mo
  - 32%: > 24 mo

Coron Artery Dis. 2013;24:217-23.

Longer vs shorter DAPT in Cypher Vs. Endeavor

- **2,141 patients receiving SES and ZES**
  - Cypher/Endeavor: 50/50%
  - SA/other/UA-NSTEMI/STEMI/other: 10/9/60/21%

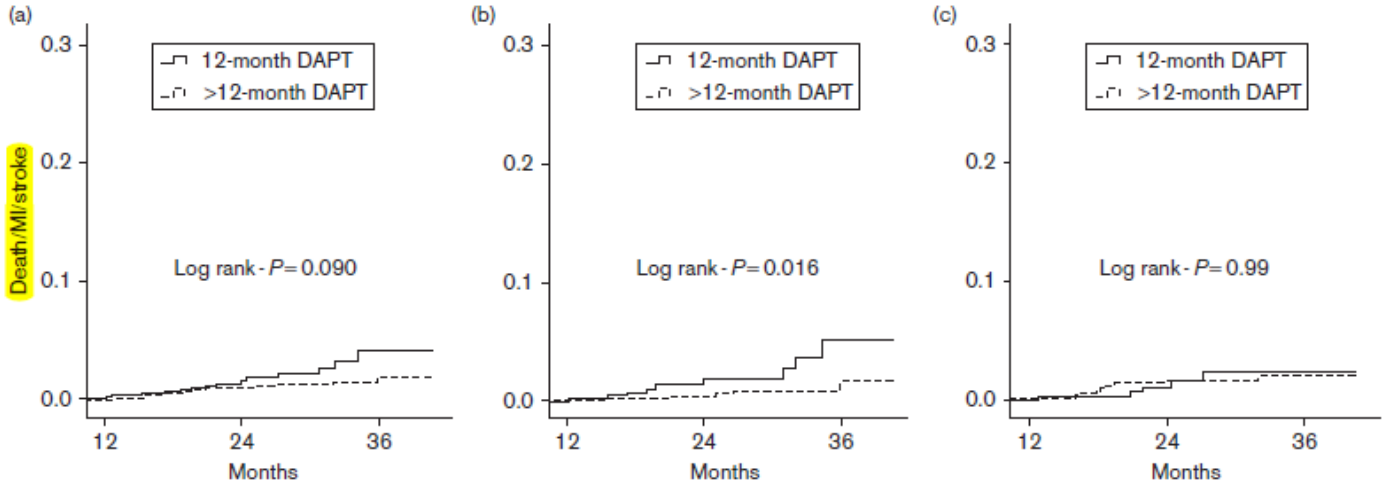
Table 1 Baseline clinical characteristics of patients according to different durations of dual antiplatelet therapy

Variables	12-month DAPT	>12-month DAPT	*P* value
Patients (*n*)	772	1098	
Age (years)	58.5±10.5	58.5±11.0	0.98
EF (%)	62.2±9.3	62.3±8.9	0.80
Male [*n* (%)]	585 (75.8)	844 (76.9)	0.59
Hypertension [*n* (%)]	438 (56.7)	667 (60.7)	0.08
Hyperlipidemia [*n* (%)]	118 (15.3)	173 (15.8)	0.78
Smoking history [*n* (%)]	318 (41.2)	444 (40.4)	0.74
Diabetes mellitus [*n* (%)]	183 (23.7)	325 (29.6)	0.005
Prior MI [*n* (%)]	91 (11.8)	112(10.2)	0.28
Prior PCI [*n* (%)]	69 (8.9)	112 (10.2)	0.36
Prior CVD [*n* (%)]	53 (6.9)	66 (6.0)	0.46
Type of DES [*n* (%)]			0.14
SES	410 (53.1)	545 (49.6)	
ZES	362 (46.9)	553 (50.4)	
Indication for PCI [*n* (%)]			0.54
SAP	80 (10.4)	109 (9.9)	
NSTEMI/UAP	475 (61.5)	653 (59.5)	
STEMI	164 (21.2)	265 (24.1)	
Other	53 (6.9)	71 (6.5)	
Multivessel disease [*n* (%)]	359 (46.5)	491 (44.7)	0.45
Number of stents implanted	1.55±0.84	1.63±0.95	0.046
Number of treated lesions	1.34±0.63	1.36±0.66	0.60

Coron Artery Dis. 2013;24:217-23.

Longer vs shorter DAPT in Cypher Vs. Endeavor

- **2,141 patients receiving SES and ZES**
  - All enrollee, Cypher group, and Endeavor group



Cumulative incidence of the composite of death, myocardial infarction (MI), and stroke in (a) the entire population enrolled in our study; (b) patients implanted with sirolimus-eluting stents; and (c) patients implanted with zotarolimus-eluting stents. DAPT, dual antiplatelet therapy.

Coron Artery Dis. 2013;24:217-23.

Longer vs shorter DAPT in Cypher Vs. Endeavor

- 2,141 patients receiving SES and ZES

Table 3 Univariate and multivariate baseline predictors of the composite of death, myocardial infarction, and stroke in patients implanted with drug-eluting stents

	HR (95% CI) *P* value					
	Overall patients		Patients treated with SES		Patients treated with ZES	
Variables	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
12-month DAPT	1.90 (0.89–4.02) 0.095	2.10 (0.94–4.51) 0.07	3.62 (1.19–11.0) 0.023	3.56 (1.18–10.8) 0.025	1.00 (0.33–3.01) 0.996	0.89 (0.29–2.72) 0.84
Age	1.08 (1.04–1.13) <0.001	1.08 (1.04–1.13) <0.001	1.08 (1.02–1.15) 0.009	1.09 (1.03–1.15) 0.01	1.08 (1.01–1.14) 0.005	1.07 (1.01–1.14) 0.021
EF	0.97 (0.94–1.01) 0.10	–	0.99 (0.94–1.06) 0.93	–	0.95 (0.91–1.00) 0.04	0.97 (0.93–1.01) 0.084
Diabetes	1.96 (0.93–4.15) 0.078	1.80 (0.84–3.84) 0.13	1.41 (0.47–4.20) 0.54	–	2.66 (0.93–7.60) 0.067	2.05 (0.71–5.94) 0.19
Hypertension	1.03 (0.48–2.21) 0.93	–	1.56 (0.49–4.99) 0.45	–	0.72 (0.25–2.05) 0.54	–
Number of stents implanted	1.16 (0.81–1.66) 0.42	–	0.95 (0.53–1.70) 0.86	–	1.36 (0.85–2.18) 0.20	–
Multivessel disease	1.95 (0.91–4.17) 0.08	1.53 (0.71–3.28) 0.28	1.26 (0.44–3.58) 0.67	–	3.04 (0.95–9.70) 0.06	2.02 (0.61–6.64) 0.25
Prior MI	1.35 (0.47–3.88) 0.58	–	1.30 (0.29–5.83) 0.73	–	1.38 (0.31–6.16) 0.68	–

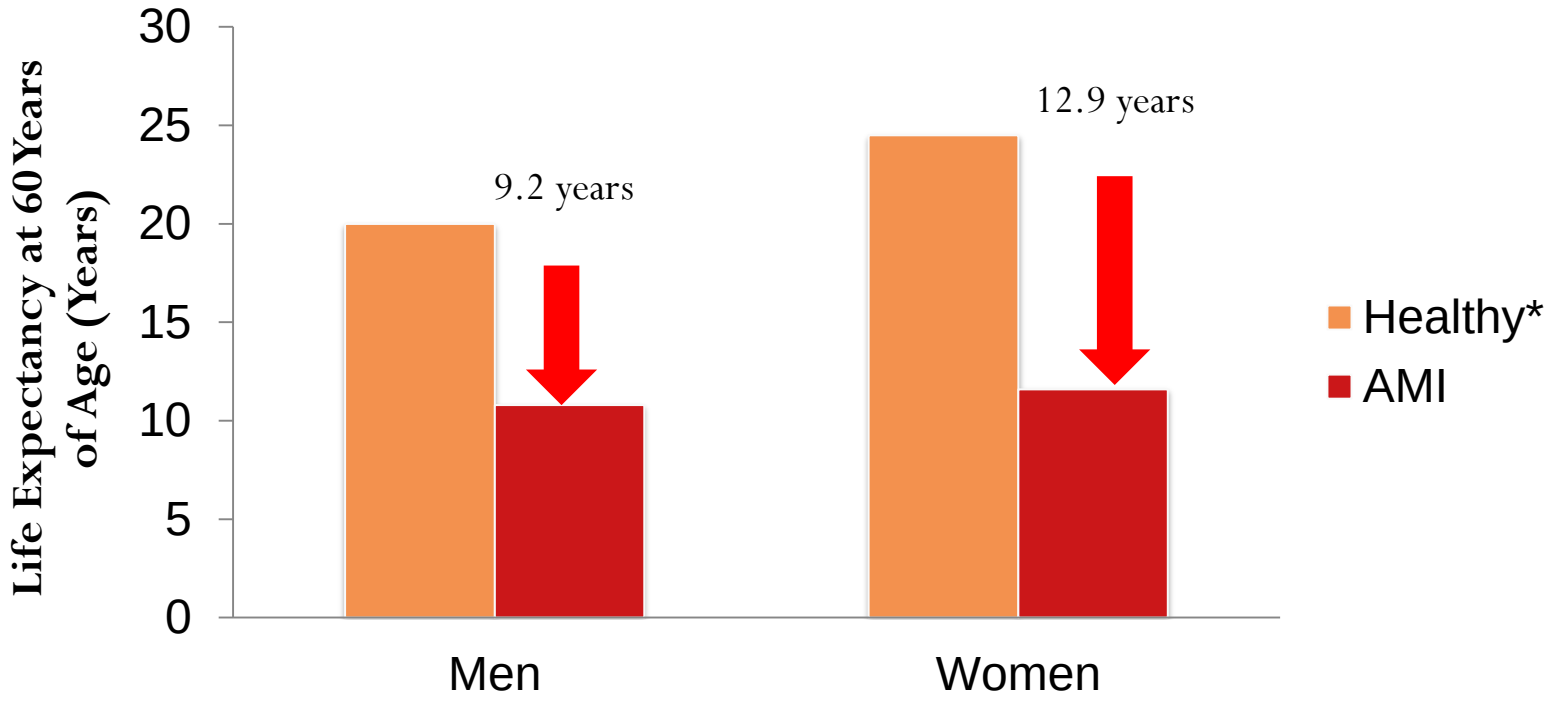
CI, confidence interval; DAPT, dual antiplatelet therapy; EF, ejection fraction; HR, hazards ratio; MI, myocardial infarction; SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent.

Coron Artery Dis. 2013;24:217-23.

In the case of ACS ….

ACS… remained CV risk

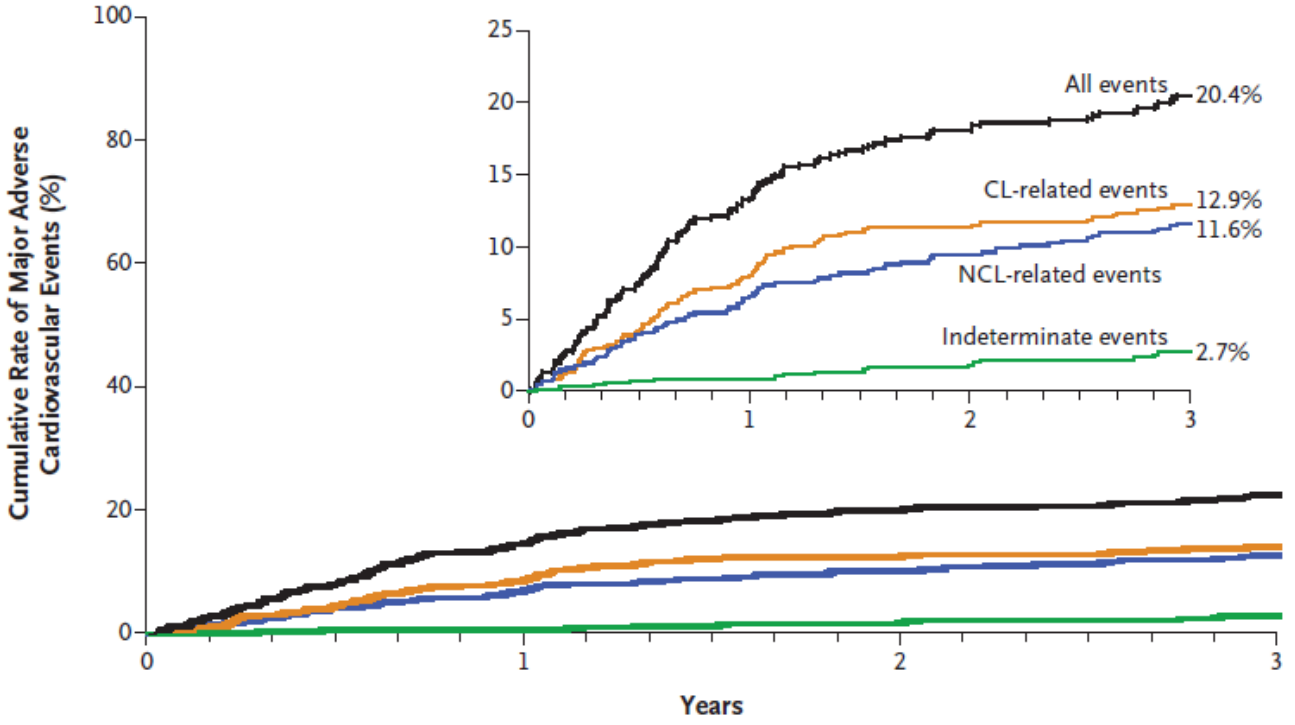
- **Framingham heart study cohort**
  - 5,000 residents aged 28~62 year old (1948-1991)



Eur Heart J. 2002;23:458-466

ACS… remained CV risk

- **PROSPECT registry**
  - 3.4 year observation after ACS PCI (n=697)
    - MACE rate: 20.4%, CV death: 4.9%



No. at Risk				
All patients	697	557	506	480
Patients with CL-related events	697	590	543	518
Patients with NCL-related events	697	595	553	521
Patients with indeterminate events	697	634	604	583

N Engl J Med. 2011;364:226-35.

TIMI38-TRITON

- **Prasugrel showed better performance than clopdiogrel.**
  - 13,608 moderate to high risk of ACS (UA or NSTEMI: 74%, PCI 99%)

Table 2. Major Efficacy End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6813)	Clopidogrel (N=6795)	Hazard Ratio for Prasugrel (95% CI)	P Value†
	no. of patients (%)			
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary end point)	643 (9.9)	781 (12.1)	0.81 (0.73–0.90)	<0.001
Death from cardiovascular causes	133 (2.1)	150 (2.4)	0.89 (0.70–1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67–0.85)	<0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71–1.45)	0.93
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78–1.16)	0.64
Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization	652 (10.0)	798 (12.3)	0.81 (0.73–0.89)	<0.001
Death from any cause, nonfatal MI, or nonfatal stroke	692 (10.7)	822 (12.7)	0.83 (0.75–0.92)	<0.001
Urgent target-vessel revascularization	156 (2.5)	233 (3.7)	0.66 (0.54–0.81)	<0.001
Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia	797 (12.3)	938 (14.6)	0.84 (0.76–0.92)	<0.001
Stent thrombosis‡	68 (1.1)	142 (2.4)	0.48 (0.36–0.64)	<0.001

N Engl J Med. 2007;357:2001-15.

TIMI38-TRITON

- **Prasugrel: high rate of bleeding compared to clopidogrel**
  - 13,608 moderate to high risk of ACS (UA or NSTEMI: 74%, PCI 99%)

Table 3. Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6741)	Clopidogrel (N=6716)	Hazard Ratio for Prasugrel (95% CI)	P Value
	no. of patients (%)			
Non–CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77–1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09–2.08)	0.01
Related to trauma	9 (0.2)	12 (0.2)	0.75 (0.32–1.78)	0.51
Life-threatening†	85 (1.4)	56 (0.9)	1.52 (1.08–2.13)	0.01
Related to instrumentation	28 (0.5)	18 (0.3)	1.55 (0.86–2.81)	0.14
Spontaneous	50 (0.9)	28 (0.5)	1.78 (1.12–2.83)	0.01
Related to trauma	7 (0.1)	10 (0.2)	0.70 (0.27–1.84)	0.47
Fatal‡	21 (0.4)	5 (0.1)	4.19 (1.58–11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87–1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

N Engl J Med. 2007;357:2001-15.

PLATO

- **Ticagrelor showed better performance than clopdiogrel.**
  - 18,624 ACS (UA or NSTEMI: 62%, PCI 64%, CABG 10%)

Table 3. Major Efficacy End Points at 12 Months.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001‡
Secondary end points — no./total no. (%)				
Death from any cause, MI, or stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77–0.92)	<0.001‡
Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event	1290/9333 (14.6)	1456/9291 (16.7)	0.88 (0.81–0.95)	<0.001‡
MI	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75–0.95)	0.005‡
Death from vascular causes	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69–0.91)	0.001‡
Stroke	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91–1.52)	0.22
Ischemic	96/9333 (1.1)	91/9291 (1.1)		0.74
Hemorrhagic	23/9333 (0.2)	13/9291 (0.1)		0.10
Unknown	10/9333 (0.1)	2/9291 (0.02)		0.04
Other events — no./total no. (%)				
Death from any cause	399/9333 (4.5)	506/9291 (5.9)	0.78 (0.69–0.89)	<0.001
Death from causes other than vascular causes	46/9333 (0.5)	64/9291 (0.8)	0.71 (0.49–1.04)	0.08
Severe recurrent ischemia	302/9333 (3.5)	345/9291 (4.0)	0.87 (0.74–1.01)	0.08
Recurrent ischemia	500/9333 (5.8)	536/9291 (6.2)	0.93 (0.82–1.05)	0.22
TIA	18/9333 (0.2)	23/9291 (0.3)	0.78 (0.42–1.44)	0.42
Other arterial thrombotic event	19/9333 (0.2)	31/9291 (0.4)	0.61 (0.34–1.08)	0.09

N Engl J Med. 2009;361:1045-57.

PLATO

- **Ticagrelor: high rate of bleeding compared to clopidogrel.**
  - 18,624 ACS (UA or NSTEMI: 62%, PCI 64%, CABG 10%)

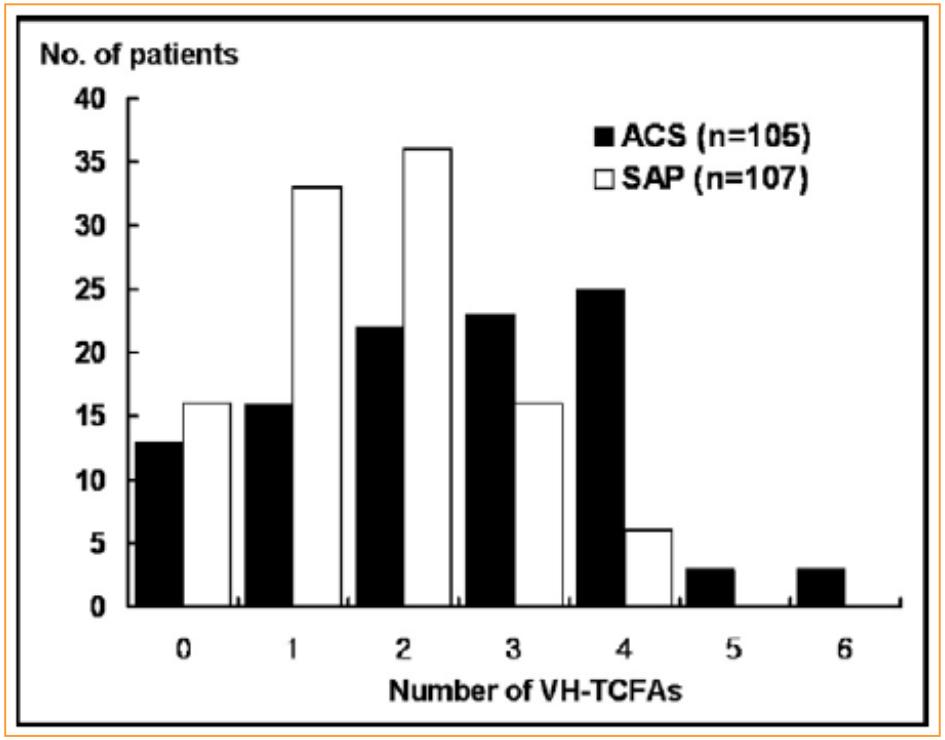
Table 4. Safety of the Study Drugs.*

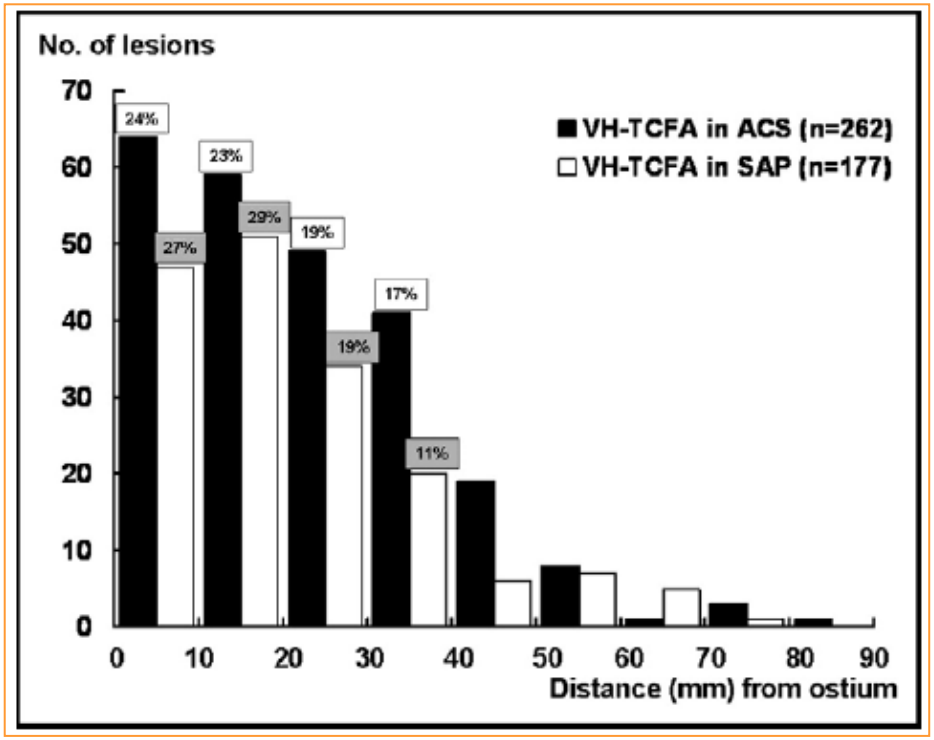
End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI)†	P Value
Primary safety end points — no./total no. (%)				
Major bleeding, study criteria	961/9235 (11.6)	929/9186 (11.2)	1.04 (0.95–1.13)	0.43
Major bleeding, TIMI criteria‡	657/9235 (7.9)	638/9186 (7.7)	1.03 (0.93–1.15)	0.57
Bleeding requiring red-cell transfusion	818/9235 (8.9)	809/9186 (8.9)	1.00 (0.91–1.11)	0.96
Life-threatening or fatal bleeding, study criteria	491/9235 (5.8)	480/9186 (5.8)	1.03 (0.90–1.16)	0.70
Fatal bleeding	20/9235 (0.3)	23/9186 (0.3)	0.87 (0.48–1.59)	0.66
Nonintracranial fatal bleeding	9/9235 (0.1)	21/9186 (0.3)		0.03
Intracranial bleeding	26/9235 (0.3)	14/9186 (0.2)	1.87 (0.98–3.58)	0.06
Fatal	11/9235 (0.1)	1/9186 (0.01)		0.02
Nonfatal	15/9235 (0.2)	13/9186 (0.2)		0.69
Secondary safety end points — no./total no. (%)				
Non–CABG-related major bleeding, study criteria	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non–CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria‡	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33
Dyspnea — no./total no. (%)				
Any	1270/9235 (13.8)	721/9186 (7.8)	1.84 (1.68–2.02)	<0.001
Requiring discontinuation of study treatment	79/9235 (0.9)	13/9186 (0.1)	6.12 (3.41–11.01)	<0.001

N Engl J Med. 2009;361:1045-57.

ACS, disease of multiple vulnerable plaques

- **VH-IVS on 3 vessels**



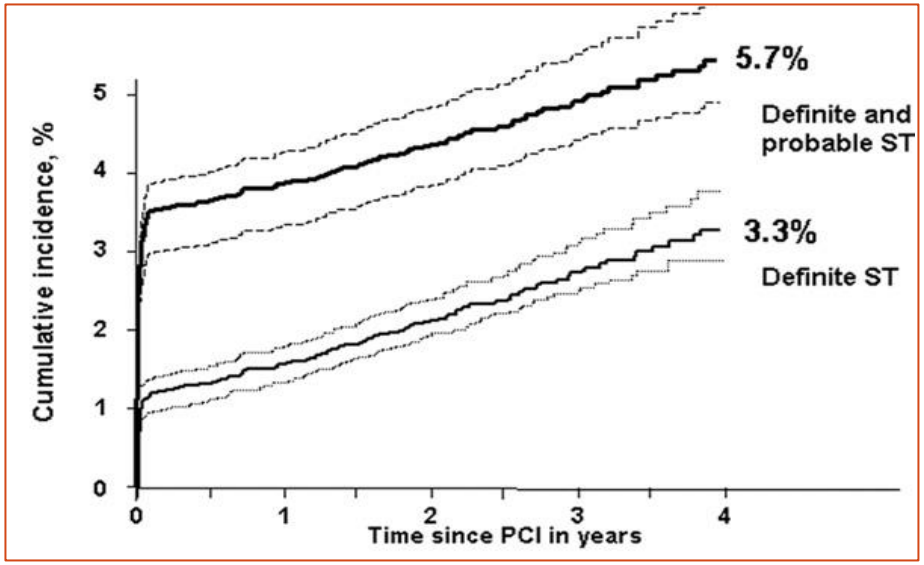


Am J Cardiol. 2008;101:568-72

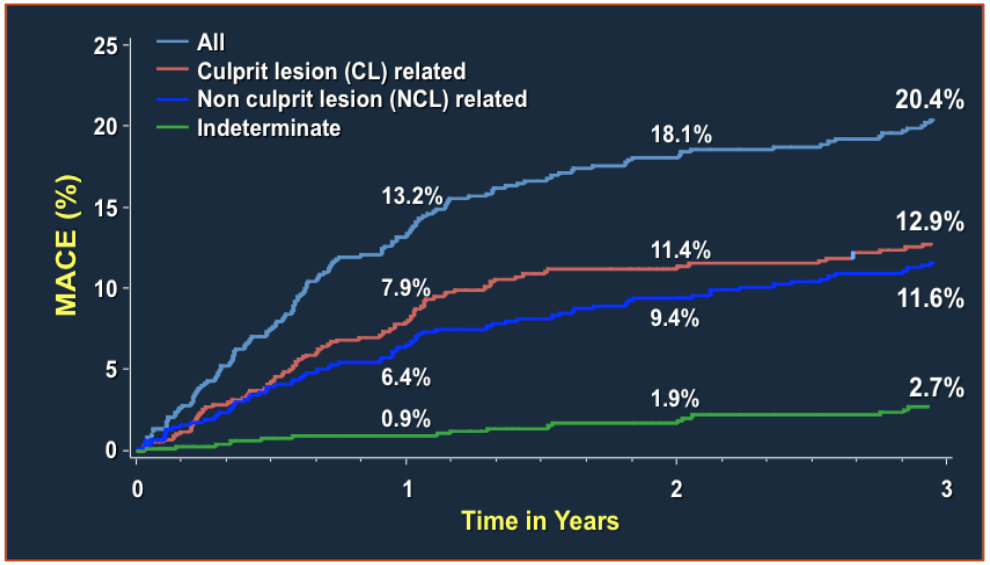
1 year of DAPT: is that reasonable?

- **Risk of stent thrombosis, MACE after ACS never stops ..**

  - **Definite stent thrombosis**



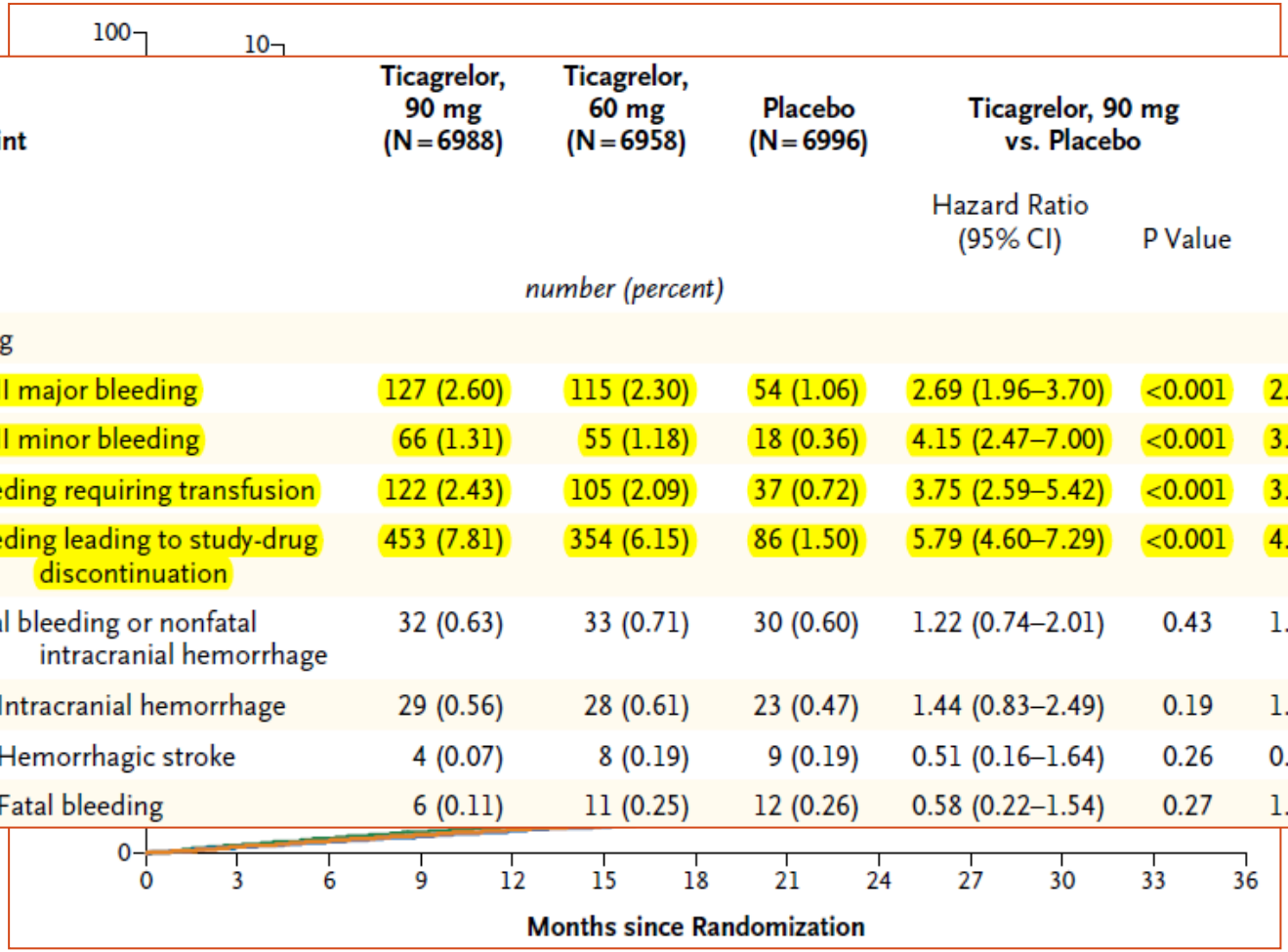
MACE after PCI for ACS



J Am Coll Cardiol. 2008;52:1134-40.
N Engl J Med. 2011;364:226-35.

PEGASUS-TIMI54

- **Ticagrelor: > 1yr use of DAPT reduced MACE after MI.**
  - 21,161 stabilized AMI (at least 1 year) patients ACS (NSTEMI: 41%)



End Point	Ticagrelor, 90 mg (N=6988)	Ticagrelor, 60 mg (N=6958)	Placebo (N=6996)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Bleeding							
TIMI major bleeding	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96–3.70)	<0.001	2.32 (1.68–3.21)	<0.001
TIMI minor bleeding	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47–7.00)	<0.001	3.31 (1.94–5.63)	<0.001
Bleeding requiring transfusion	122 (2.43)	105 (2.09)	37 (0.72)	3.75 (2.59–5.42)	<0.001	3.08 (2.12–4.48)	<0.001
Bleeding leading to study-drug discontinuation	453 (7.81)	354 (6.15)	86 (1.50)	5.79 (4.60–7.29)	<0.001	4.40 (3.48–5.57)	<0.001
Fatal bleeding or nonfatal intracranial hemorrhage	32 (0.63)	33 (0.71)	30 (0.60)	1.22 (0.74–2.01)	0.43	1.20 (0.73–1.97)	0.47
Intracranial hemorrhage	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83–2.49)	0.19	1.33 (0.77–2.31)	0.31
Hemorrhagic stroke	4 (0.07)	8 (0.19)	9 (0.19)	0.51 (0.16–1.64)	0.26	0.97 (0.37–2.51)	0.94
Fatal bleeding	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22–1.54)	0.27	1.00 (0.44–2.27)	1.00

N Engl J Med. 2009;361:1045-57.

2014 ESC guideline for myocardial revascularization

- **STEMI**

Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy			
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.) and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	776,794
A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A	–
• Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication	I	B	828
• Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication	I	B	823
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B	812
It is recommended to give $P2Y_{12}$ inhibitors at the time of first medical contact.	I	B	777,846–848
GP IIb/IIIa inhibitors should be considered for bail-out or evidence of no-reflow or a thrombotic complication.	IIa	C	–
Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.	IIb	B	271,834, 835,849

Eur Heart J. 2014;35:2541-619.

2014 ESC guideline for myocardial revascularization

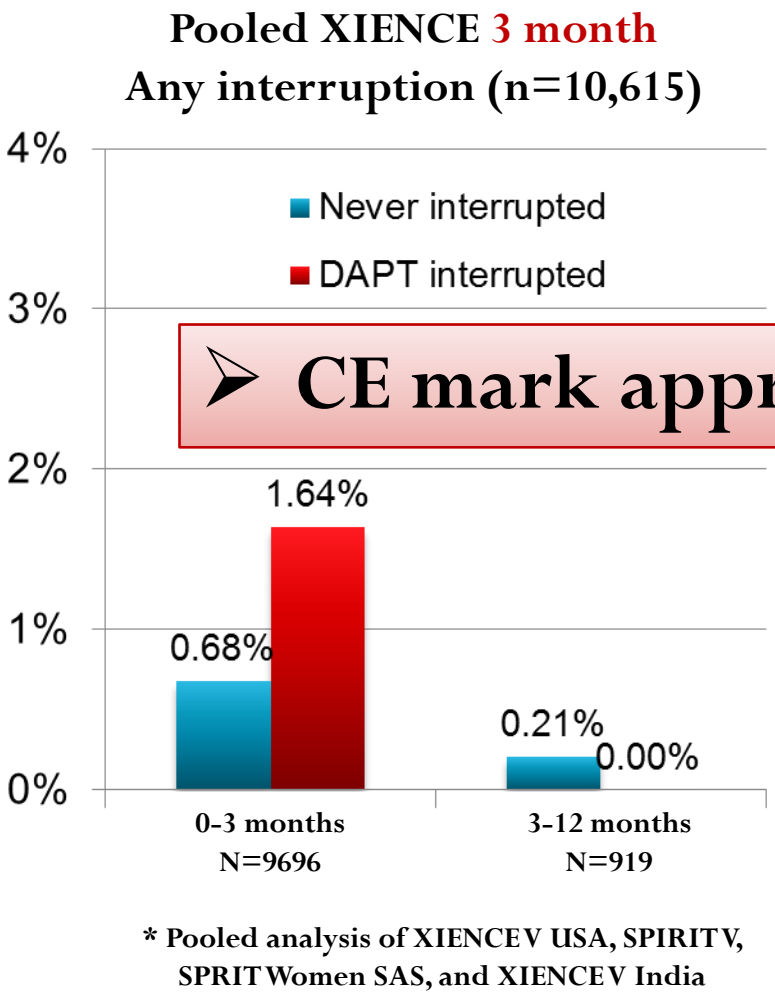
- **NSTEMI**

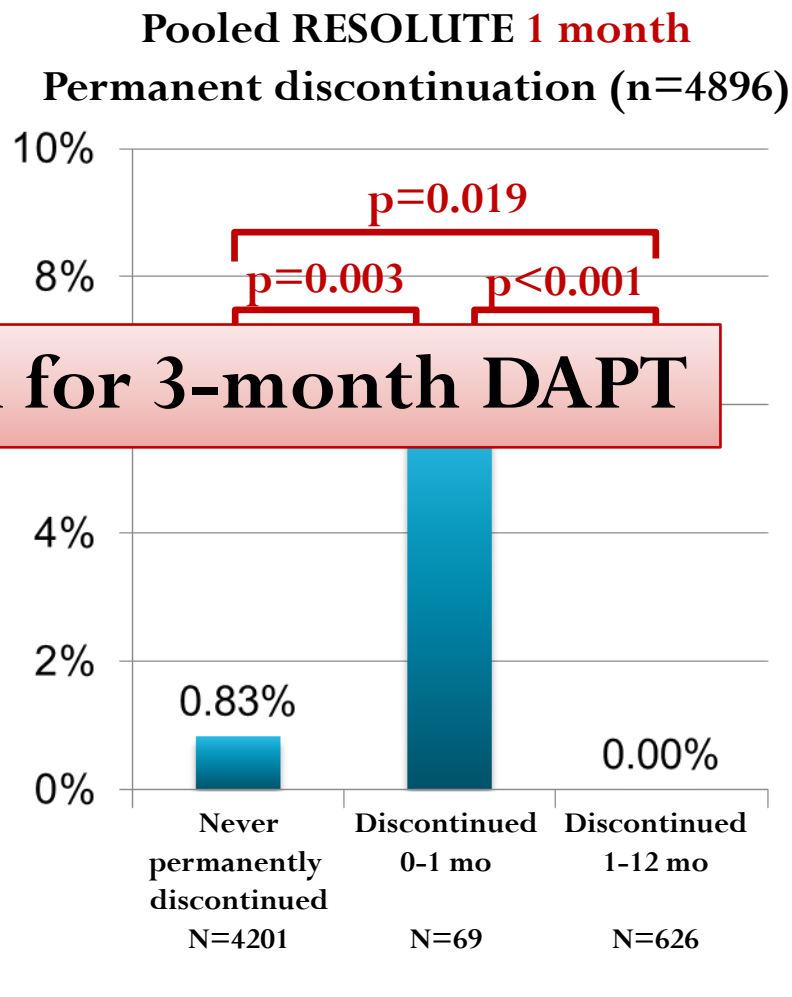
Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy			
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	774,776,794
A $P2Y_{12}$ inhibitor is recommended in addition to ASA, and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A	337,341,825
• Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication.	I	B	337
• Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication.	I	B	341
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B	812,825
GP IIb/IIIa antagonists should be considered for bail-out situation or thrombotic complications.	IIa	C	
Pre-treatment with prasugrel in patients in whom coronary anatomy not known, is not recommended.	III	B	826
Pre-treatment with GP IIb/IIIa antagonists in patients in not known, is not recommended.	III	A	357,815

Eur Heart J. 2014;35:2541-619.

Short DAPT Duration for Current DES?

3-month DAPT for EES and 1-month for R-ZES





➢ CE mark approval for 3-month DAPT

* Pooled analysis of XIENCE V USA, SPIRIT V, SPRIT Women SAS, and XIENCE V India

Modified from Stone G, TCT 2012, and Kirtane AJ, ESC 2012

RESET: Primary Endpoint on 1 year

3 months use of DAPT in ZES

- **SA/UA/AMI: 45/40/15% (n=2,117)**
  - Endeavor + 3 Mo DAPT vs Cypher/Xience/Resolute + 12 Mo DAPT

Characteristics	E-ZES+3-Month DAPT (n = 997)	Standard Therapy (n = 1,058)	Difference (95% CI)	p Value
Composite events				
Primary endpoint	36 (4.6)	41 (4.7)	−0.1% (−2.7 to 2.4)	0.69
Death from any cause, myocardial infarction, or stent thrombosis	6 (0.6)	11 (1.3)	−0.7% (−1.6 to 0.3)	0.27
Death from cardiovascular cause or myocardial infarction	4 (0.4)	7 (0.7)	−0.3% (−0.9 to 0.4)	0.42
Each compone				
Death				
From any				
From card				
Myocardial i				
Target vesse				
Non–target v				
Stent throm				
<1 month				
1–3 months	0	0		
3–12 months	0	3		
Bleeding				
Major or minor	5 (0.5)	10 (1.0)	−0.5% (−1.2 to 0.3)	0.24
Major	2 (0.2)	6 (0.6)	−0.4% (−0.9 to 0.2)	0.18
Cerebrovascular accidents	5 (0.5)	6 (0.7)	−0.2% (−0.9 to 0.6)	0.80
Acute coronary syndrome subset, n	301	300	—	—
Primary endpoint	12 (6.5)	6 (2.0)	4.4% (−1.4 to 10.2)	0.16
Death from cardiovascular cause	1 (0.3)	0 (0.0)		0.32
Myocardial infarction	0 (0.0)	0 (0.0)		1.00
Target vessel revascularization	9 (5.4)	2 (0.7)	4.7% (−0.8 to 10.1)	0.04
Stent thrombosis, definite or probable	1 (0.3)	0 (0.0)	−0.9% (−5.1 to 3.4)	0.32
Bleeding, major or minor	2 (0.7)	4 (1.3)	−0.7% (−2.3 to 0.9)	0.41

Values are the number of events and the cumulative event rate (%). Analysis was performed after exclusion of the patients with interrupting 3-month DAPT. *p values were calculated with the use of the log-rank test.

Abbreviations as in Tables 1 and 2.

J Am Coll Cardiol. 2012;60:1340.

SECURITY: 6- vs 12-months DAPT (n=1,399)

- 1:1 randomized, multicenter, international, investigator-driven, non-inferiority study
- Patients with a stable or unstable angina (61%, 39%), at least one of 2nd generation DES
- Stent type: Endeavor Resolute/Nobori/Biomatrix/Promus/Xience = 41/26/7.3/11/9%
- Clopidogrel/Prasugrel/Ticagrelor = 99/0.3/0.6%
- Primary Endpoint: Composite of cardiac death, MI, stroke, definite or probable stent thrombosis or BARC type 3 or 5 bleeding at 12 months.
- Secondary endpoint: Composite of cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC type 2, 3, or 5 bleeding at 12 and 24 months.

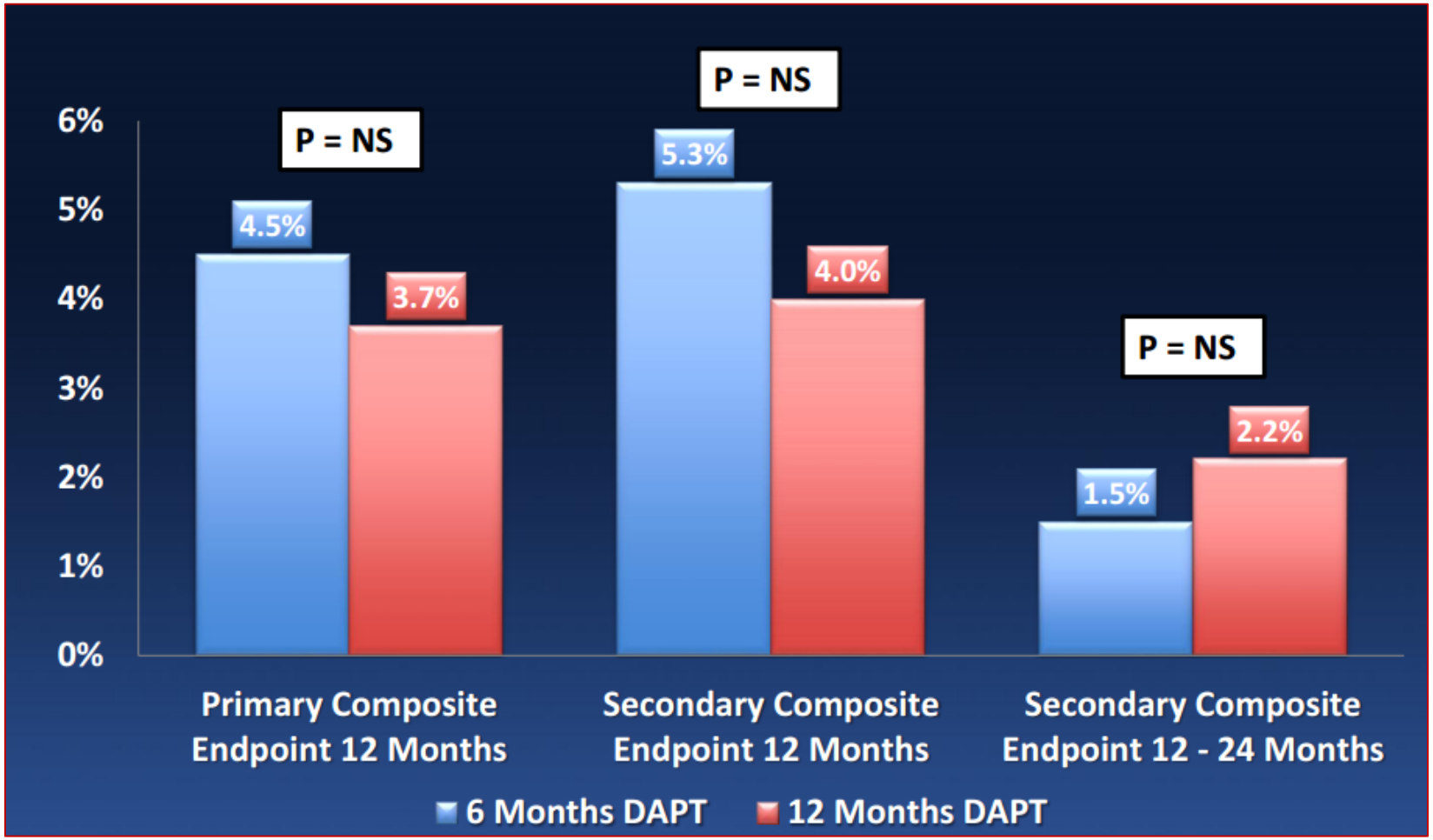
TABLE 4 Medication Use During Trial in Patients Receiving 6 Months and 12 Months of DAPT

	6-Month DAPT (n = 682)	12-Month DAPT (n = 717)
DAPT therapy at 6 months		
Clopidogrel only	2 (0.3)	6 (0.9)
ASA only	3 (0.5)	5 (0.7)
ASA + clopidogrel	618 (97.3)	655 (97.6)
ASA + prasugrel	8 (1.3)	2 (0.3)
ASA + ticagrelor	4 (0.6)	3 (0.4)
DAPT therapy at 12 months		
Clopidogrel only	11 (1.8)	8 (1.2)
ASA only	392 (63.6)	13 (2.0)
ASA + clopidogrel	208 (33.8)	622 (96.1)
ASA + prasugrel	0	1 (0.2)
ASA + ticagrelor	0	1 (0.2)
Drug therapy at 24 months		
Aspirin	525 (96.5)	563 (97.9)

Colombo A. J Am Coll Cardiol 2014;64:2086-97.

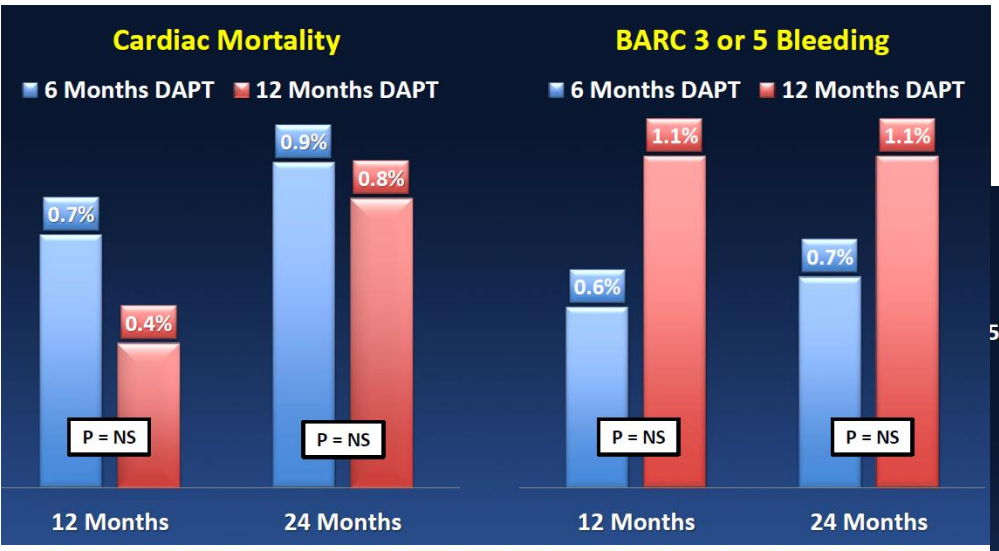
SECURITY: 6- vs 12-months DAPT (n=1,399)

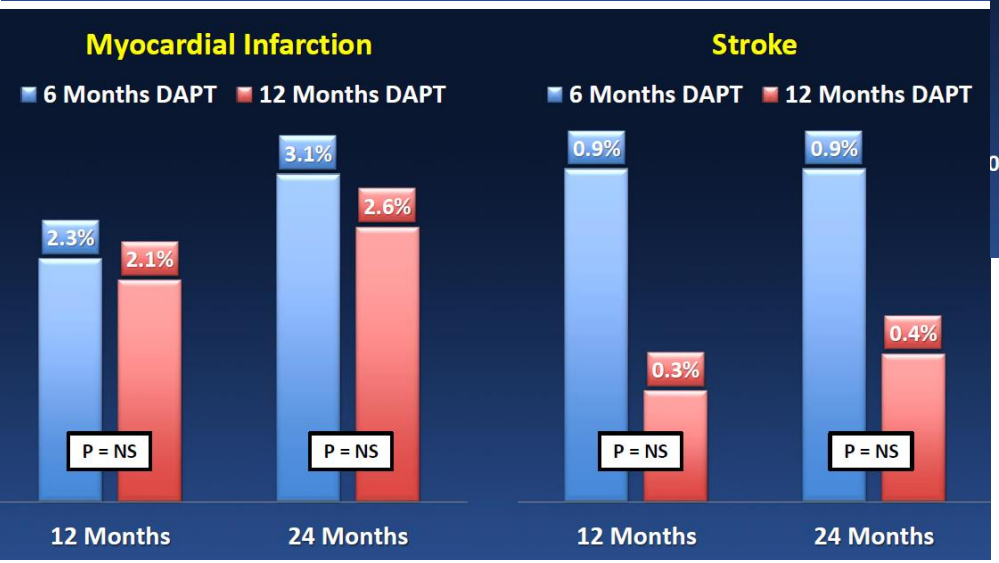
- Primary Endpoint: Composite of cardiac death, MI, stroke, definite or probable stent thrombosis or BARC type 3 or 5 bleeding at 12 months.
- Secondary endpoint: Composite of cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC type 2, 3, or 5 bleeding at 12 and 24 months.

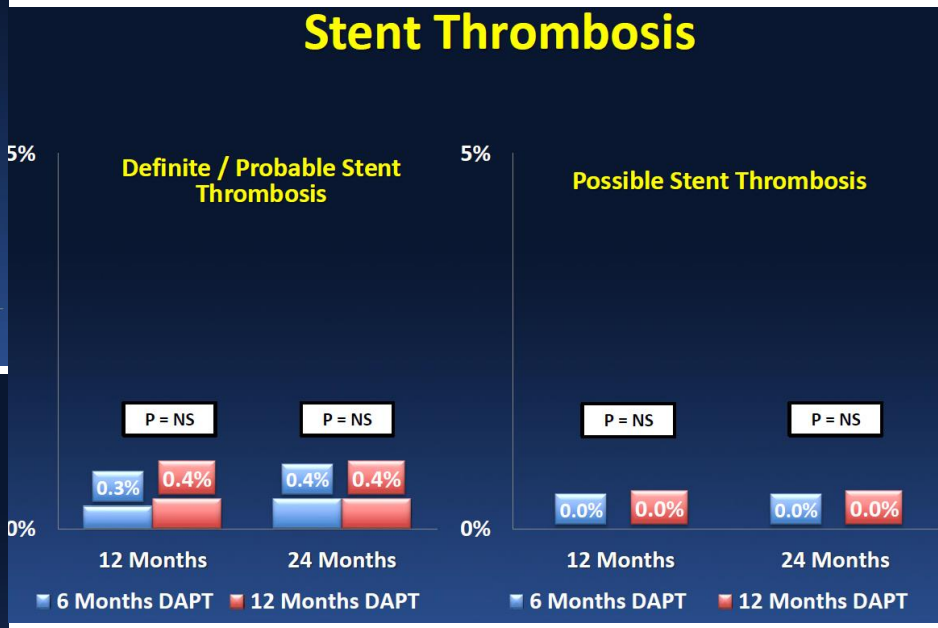


Colombo A. J Am Coll Cardiol 2014;64:2086-97.

SECURITY: 6- vs 12-months DAPT (n=1,399)







Colombo A. J Am Coll Cardiol 2014;64:2086-97.

SECURITY: predictors for PEP

TABLE 6 Predictors of the Primary Endpoint at Multivariable Analysis

Variables in the Model*	HR	95% CI	p Value
NIDDM vs. none	0.895	0.464-1.729	
IDDM vs. none	2.349	1.080-5.106	
DAPT 6- vs. 12-month	1.272	0.754-2.145	0.367
Female	1.596	0.897-2.838	0.111

*Cox model fitted on 1,360 patients with 57 primary events because of missing values.
HR = hazard ratio; other abbreviations as in Tables 1 and 5.

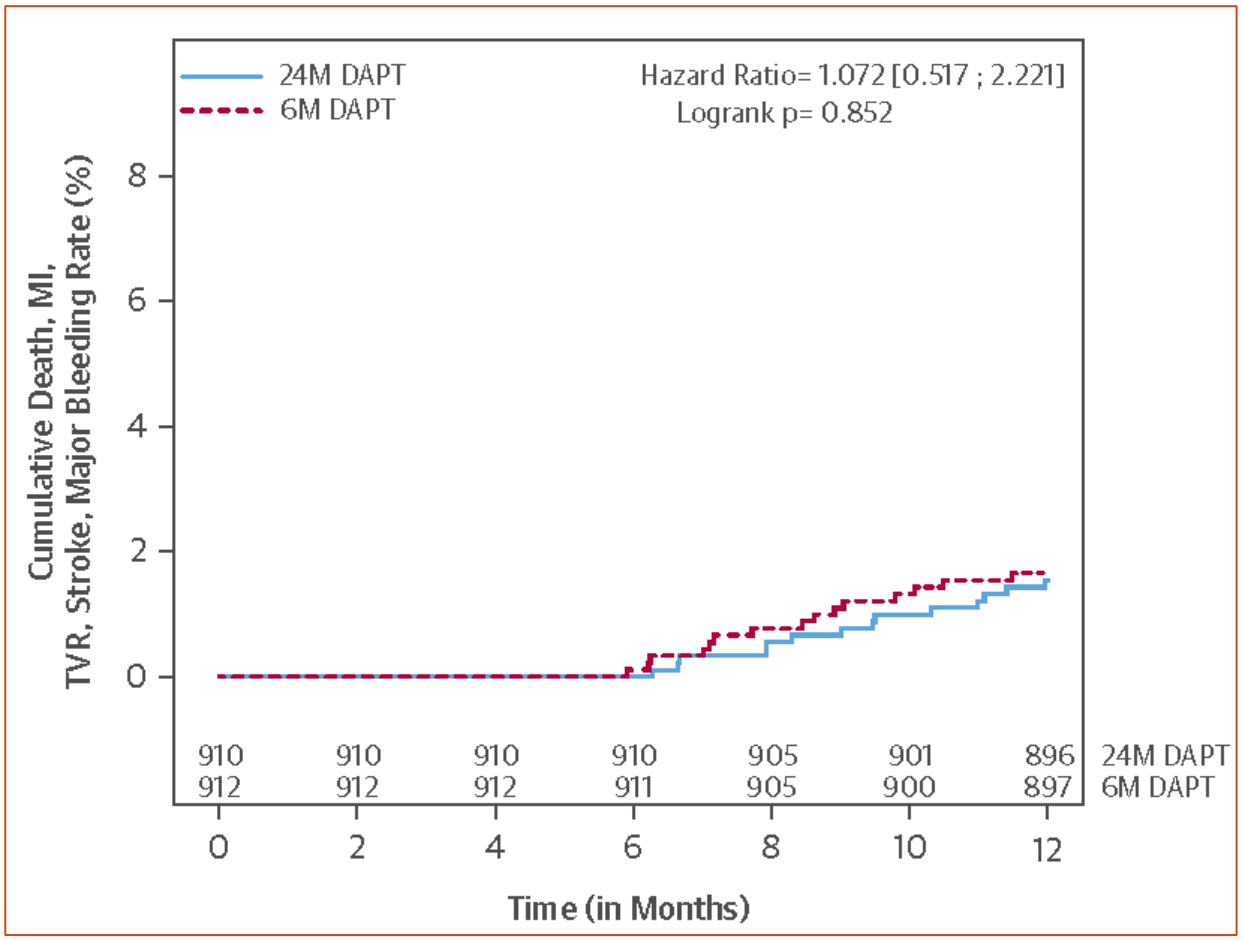
- In a low-risk population, 6 months of DAPT appeared non-inferior to a 12-month regimen with respect to the primary composite endpoint of cardiac death, MI, stroke, definite/probable ST, or BARC type 3 or 5 bleeding at 12 months.

Colombo A. J Am Coll Cardiol 2014;64:2086-97.

ITALIC: Primary Endpoint on 1 yr

New generation DES followed by 6- vs 24-months DAPT

- Prospective, open-label randomized trial conducted at 70 sites in Europe and the Middle East. (941 in 24 Mo and 953 in 6 Mo DAPT, SA+SI=60%, all Xience-V)



Clopidogrel: 98.5%
Prasugrel: 1.5%
Ticagrelor: 0%

Gilard M J Am Coll Cardiol. 2015;65:777-86.

ITALIC: Primary Endpoint on 1 yr

New generation DES followed by 6- vs 24-months DAPT

Total Population

High-Risk ACS Population

- In a low-risk population, 6 months of DAPT appeared non-inferior to a 12-month regimen with respect to the primary composite endpoint of cardiac death, MI, stroke, definite/probable ST, or BARC type 3 or 5 bleeding at 12 months.

					p Value					p Value
Primary endp from an stroke, major b					0.361					0.361
Secondary en										
Minor bleed										0.34
Minimal ble										0.66
Death										
All deaths										0.21
Cardiac death	0	3 (0.3)	3 (0.3)	1.007 (0.198-5.174)	0.48	Cardiac death	0	0	3 (0.8)	N/A
Myocardial infarction	0	4 (0.4)	6 (0.7)	1.500 (0.423-5.317)	0.53	MI	0	2 (0.5)	2 (0.5)	1.006 (0.142-7.144) 0.99
Stroke	0	4 (0.4)	0	N/A		Stroke	0	1 (0.3)	0	N/A
TVR	1 (0.8)	2 (0.2)	5 (0.5)	2.499 (0.485-12.882)	0.27	TVR	0	0	3 (0.8)	N/A 0
Stent thrombosis	0	0	3 (0.3)	N/A		Stent thrombosis	0	0	2 (0.5)	N/A
Major bleeding	0	3 (0.3)	0	N/A		Major bleeding	0	1 (0.3)	0	N/A

Values are n (%) unless otherwise indicated.

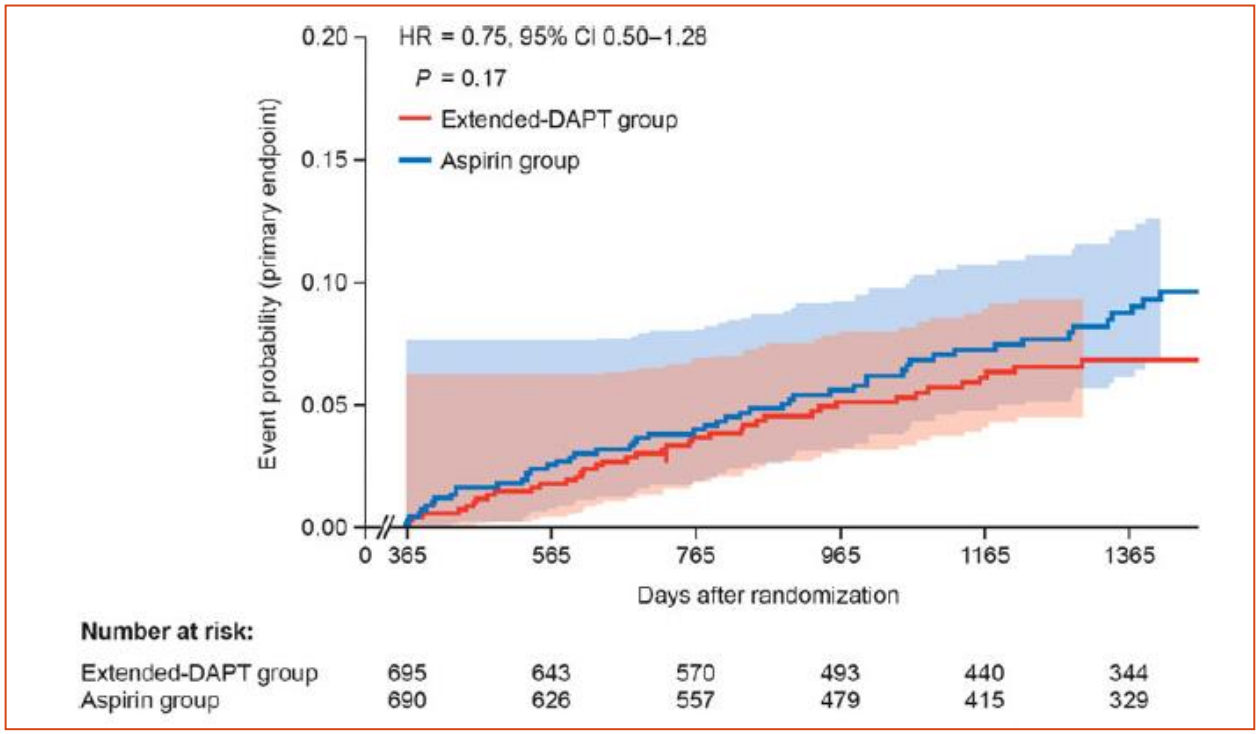
TVR = urgent target vessel revascularization

Gilard M J Am Coll Cardiol. 2015;65:777-86.

OPTIDUAL: Primary Endpoint on 33.4 mo

New generation DES followed by 12- vs 48-months DAPT

- **Design & results**
  - SA/SI/other/UA/NSTEMI/STEMI: 32/20/11/10/14/10%
  - SES/PES/ZES/EES/other: 20/15/8/50/6%
  - PEP: death, MI, stroke, major bleeding
    - MACE rate: 5.8/7.5% in 48/12 mo DAPT (p=0.17)



Helft G. Eur Heart J. 2015 Sep 12 [epub ahead of print].

OPTIDUAL: Primary Endpoint on 33.4 mo

New generation DES followed by 12- vs 48-months DAPT

- **Results**

Table 2 Clinical outcomes

Outcome, *n* (%)	Extended-DAPT group (*N* = 695)	Aspirin group (*N* = 690)	HR for extended DAPT (95% CI)	*P*-value
Primary composite outcome[a]	40 (5.8)	52 (7.5)	0.75 (0.50–1.28)	0.17
All-cause mortality	16 (2.3)	24 (3.5)	0.65 (0.34–1.22)	0.18
Cardiovascular mortality	10 (1.4)	14 (2.0)	0.69 (0.31–1.56)	0.37
Non-cardiovascular mortality	6 (0.9)	10 (1.4)	0.58 (0.21–1.61)	0.30
Non-fatal myocardial infarction	11 (1.6)	16 (2.3)	0.67 (0.31–1.44)	0.31
Non-fatal stroke	5 (0.7)	7 (1.0)	0.69 (0.22–2.18)	0.53
Ischaemic	4 (0.6)	4 (0.6)		
Haemorrhagic	1 (0.1)	2 (0.3)		
Uncertain	0 (0.0)	1 (0.1)		
Stent thrombosis				
Definite or probable	3 (0.4)	1 (0.1)	2.97 (0.31–28.53)	0.35
Definite	3 (0.4)	0 (0.0)		
Target-lesion revascularization	35 (5.0)	35 (5.1)	0.97 (0.61–1.55)	0.90
ISTH major bleeding	14 (2.0)	14 (2.0)	0.98 (0.47–2.05)	0.95

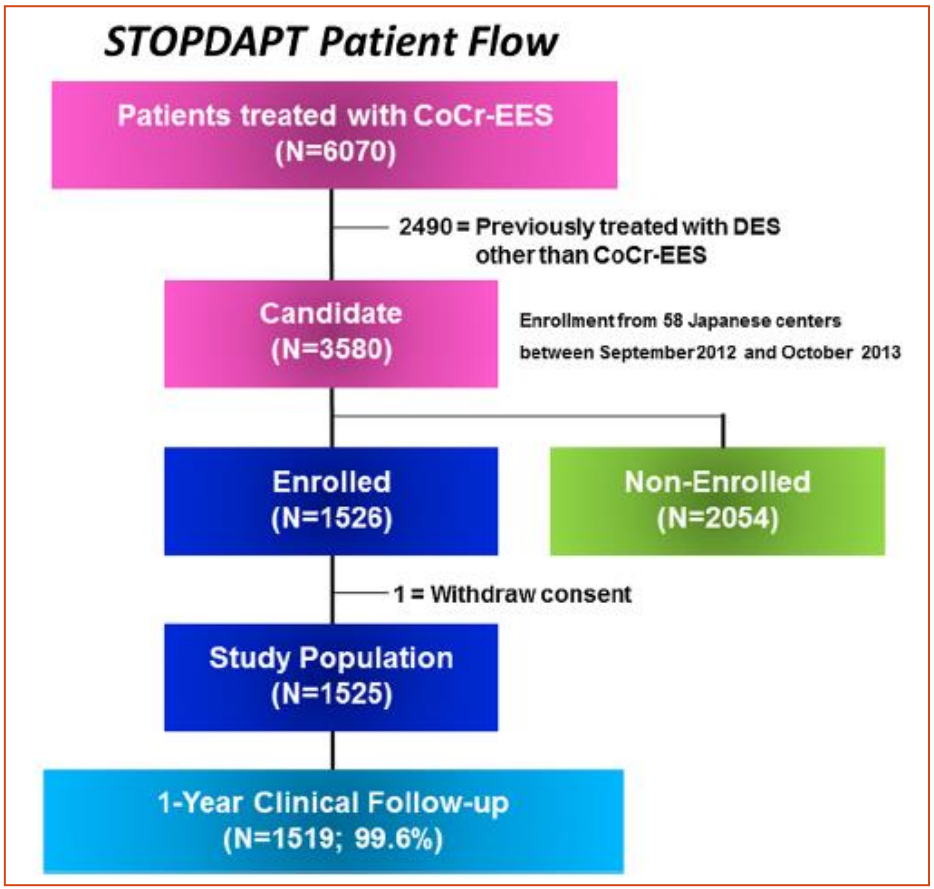
CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.
[a]Net adverse clinical events (composite of death, myocardial infarction, stroke, and major bleeding).

Helft G. Eur Heart J. 2015 Sep 12 [epub ahead of print].

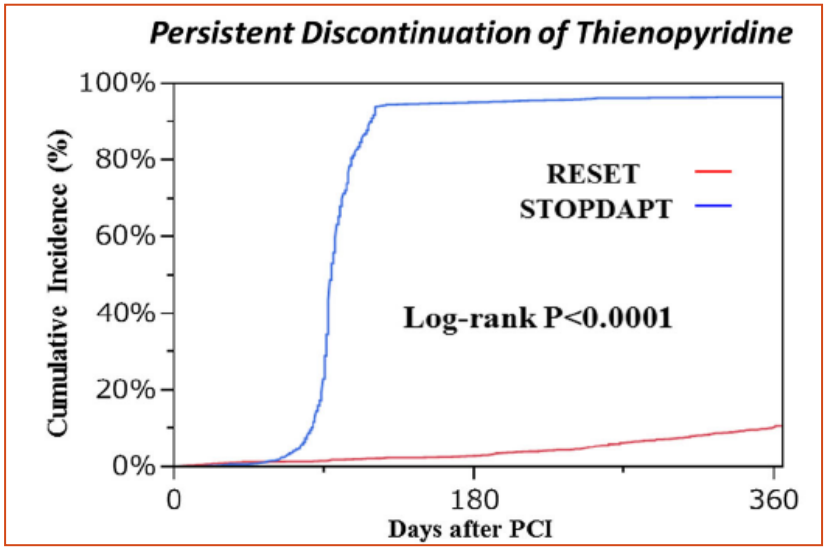
STOPDAPT: Primary Endpoint on 1 year

3 months use of DAPT in CoCr-EES

- **Design & results**



- **Follow up: 1 year**
- **Clinical presentation**
  - 68%: SCAD
  - 15%: UA
  - 17%: AMI



Natsuaki M. Cardiovasc Interv The. 2015 Oct 30 [epub ahead of print].

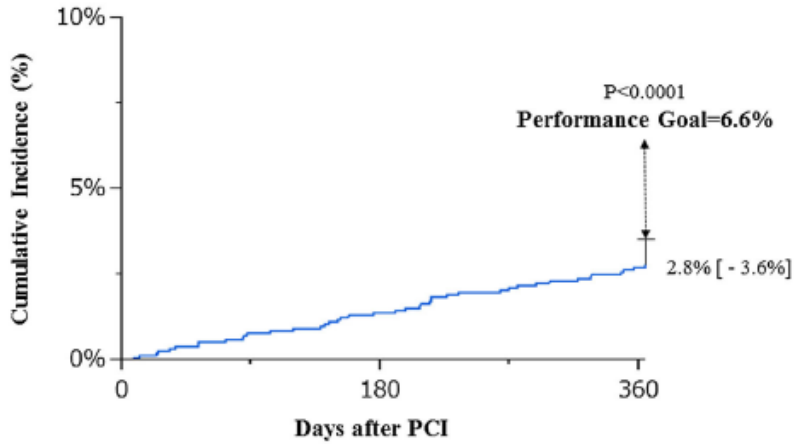
STOPDAPT: Primary Endpoint on 1 year

3 months use of DAPT in CoCr-EES

- **Results**

Primary Endpoint

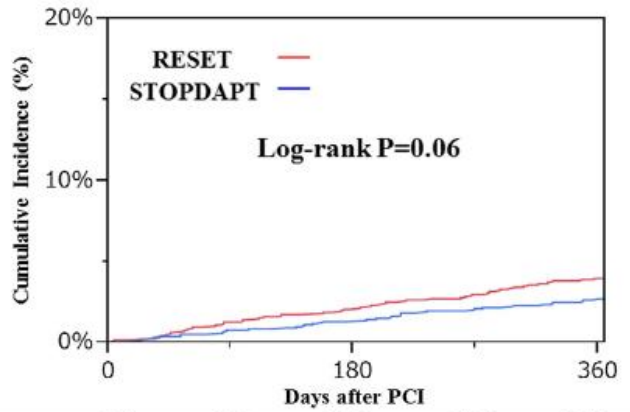
A *Cardiovascular death, MI, Stroke, Definite ST, and Bleeding*



Interval	0 day	30 days	180 days	240 days	365 days
STOPDAPT					
N of patients with at least 1 event		4	21	30	42
N of patients at risk	1525	1520	1490	1480	1458
Cumulative Incidence		0.3%	1.4%	2.0%	2.8%

Primary Endpoint

B *Cardiovascular death, MI, Stroke, Definite ST, and Bleeding*



Interval	0 day	30 days	180 days	240 days	365 days
RESET					
N of patients with at least 1 event		4	33	42	61
N of patients at risk	1559	1545	1511	1495	1209
Cumulative Incidence		0.3%	2.1%	2.7%	4.0%
STOPDAPT					
N of patients with at least 1 event		4	21	30	42
N of patients at risk	1525	1520	1490	1480	1458
Cumulative Incidence		0.3%	1.4%	2.0%	2.8%

Natsuaki M. Cardiovasc Interv The. 2015 Oct 30 [epub ahead of print].

ARCTIC-Interruption
Discontinuation of DAPT after 12 Months?

- ARCTIC was a multicenter, prospective open-label study with parallel trial arms and double randomization. Excluded patients with STEMI … 90% of clopidogrel and 10% of prasugrel.
- Patients (aged ≥18 years) scheduled for planned DES implantation at 38 centres in France.

- No apparent benefit but instead harm with extension of DAPT beyond 1 year after stenting with DES when no event has occurred within the first year after stenting.

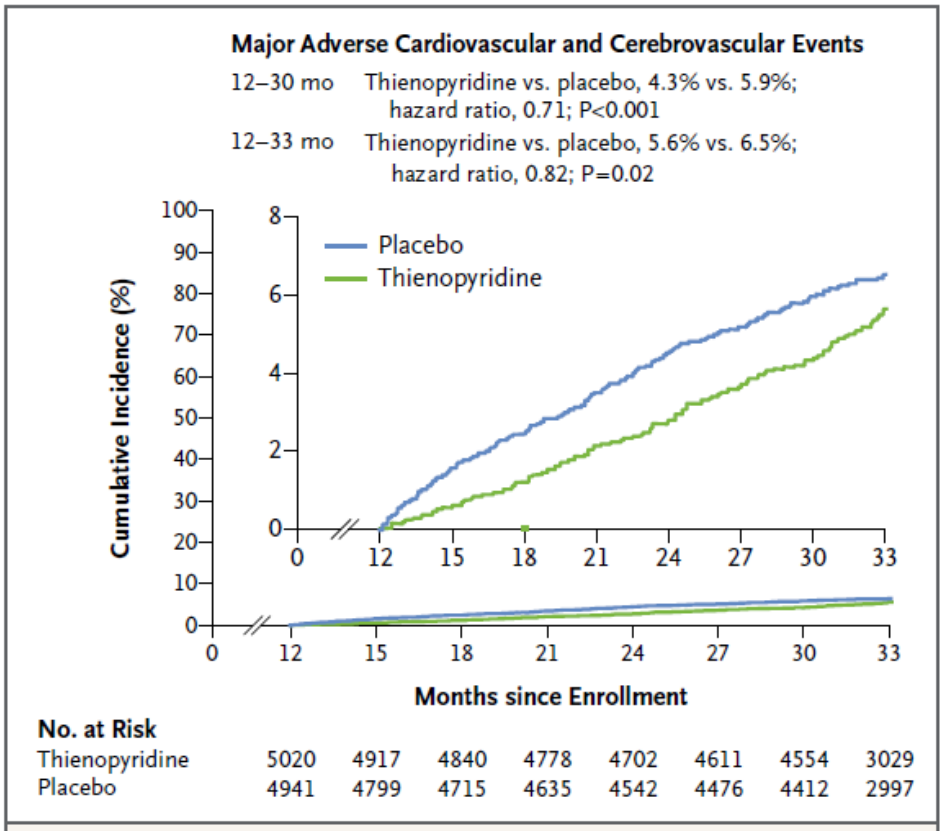
	DAPT	SAPT	HR [95%CI]	P
Stroke or TIA (%)	1	1	0.69 [0.19;2.44]	0.57
Urgent revascularization (%)	1	1	1.17 [0.45 ;3.04]	0.74
STEEPLE Major bleeding (%)	1	<0.5	0.15 [0.02; 1.20]	0.07
STEEPLE Minor bleeding (%)	1	<0.5	0.41 [0.08 ;2.13]	0.29
STEEPLE Major or minor bleeding (%)	2	1	0.26 [0.07 ;0.91]	0.04

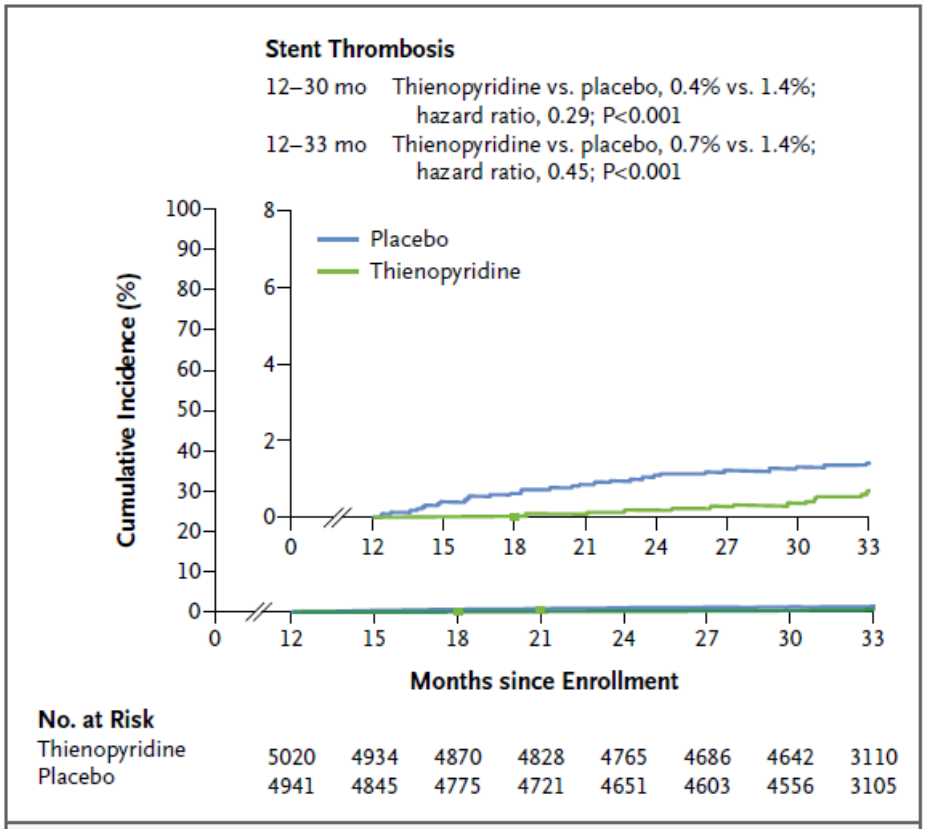
*Any death, Myocardial infarction, stent thrombosis, stroke or transient ischemic attack, urgent revascularization

Collet JP. Lancet. 2014;384:1577-85.

DAPT : Co-Primary Effectiveness Endpoint

- 9,961 patients were randomized to continued P2Y12 blocker (clopid/prasu) vs PCB on aspirin after 12 months of DAPT (12 vs 30 months)
- SA/UA/NSTEMI/STEMI = 37.8/16.7/15.5/10.5%, EES/ZES = 58%, SES/PES = 37%





Mauri L. N Engl J Med 2014;371:2155-66.

DAPT : Co-Primary Effectiveness Endpoint

- 9,961 patients were randomized to continued P2Y12 blocker (clopid/prasu) vs PCB on aspirin after 12 months of DAPT (12 vs 30 months)
- SA/other/UA/NSTEMI/STEMI = 37.8/19.7/16.7/15.5/10.5%,
- EES/ZES/PES/SES = 46.7/12.8/26.9/11.5%

Table 3. Bleeding End Point during Month 12 to Month 30.*

Bleeding Complications	Continued Thienopyridine (N=4710)	Placebo (N=4649)	Difference	Two-Sided P Value for Difference
	no. of patients (%)		*percentage points (95% CI)*	
GUSTO severe or moderate†	119 (2.5)	73 (1.6)	1.0 (0.4 to 1.5)	0.001
Severe	38 (0.8)	26 (0.6)	0.2 (–0.1 to 0.6)	0.15
Moderate	81 (1.7)	48 (1.0)	0.7 (0.2 to 1.2)	0.004
BARC type 2, 3, or 5	263 (5.6)	137 (2.9)	2.6 (1.8 to 3.5)	<0.001
Type 2	145 (3.1)	72 (1.5)	1.5 (0.9 to 2.1)	<0.001
Type 3	122 (2.6)	68 (1.5)	1.1 (0.6 to 1.7)	<0.001
Type 5	7 (0.1)	4 (0.1)	0.1 (–0.1 to 0.2)	0.38

Mauri L. N Engl J Med 2014;371:2155-66.

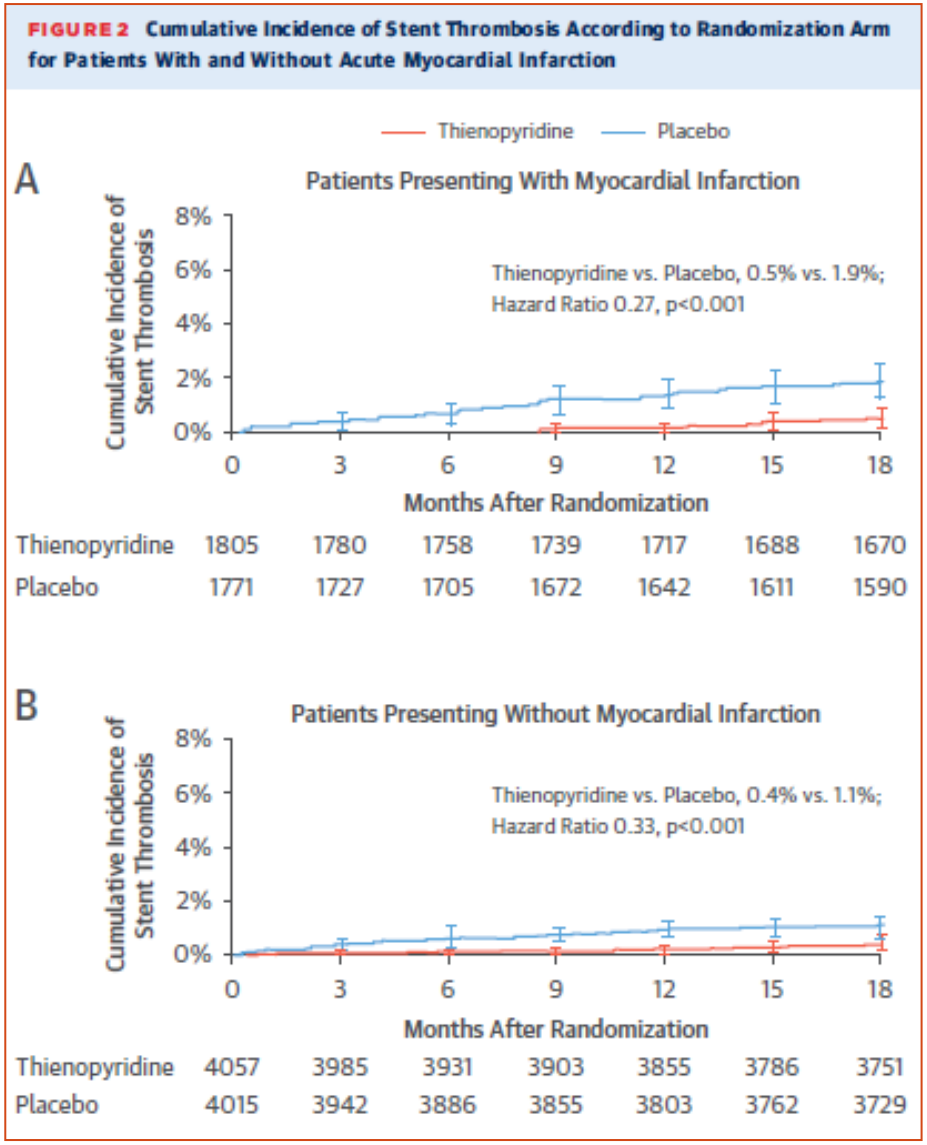
DAPT : Co-Primary Effectiveness Endpoint

Table 2. Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events.*

Outcome	Continued Thienopyridine (N=5020)	Placebo (N=4941)	Hazard Ratio, Thienopyridine vs. Placebo (95% CI)†	P Value†
	no. of patients (%)			
Stent thrombosis‡	19 (0.4)	65 (1.4)	0.29 (0.17–0.48)	<0.001
Definite	15 (0.3)	58 (1.2)	0.26 (0.14–0.45)	<0.001
Probable	5 (0.1)	7 (0.1)	0.71 (0.22–2.23)	0.55
Major adverse cardiovascular and cerebrovascular events§	211 (4.3)	285 (5.9)	0.71 (0.59–0.85)	<0.001
Death	98 (2.0)	74 (1.5)	1.36 (1.00–1.85)	0.05
Cardiac	45 (0.9)	47 (1.0)	1.00 (0.66–1.52)	0.98
Vascular	5 (0.1)	5 (0.1)	0.98 (0.28–3.39)	0.98
Noncardiovascular	48 (1.0)	22 (0.5)	2.23 (1.32–3.78)	0.002
Myocardial infarction	99 (2.1)	198 (4.1)	0.47 (0.37–0.61)	<0.001
Stroke	37 (0.8)	43 (0.9)	0.80 (0.51–1.25)	0.32
Ischemic	24 (0.5)	34 (0.7)	0.68 (0.40–1.17)	0.16
Hemorrhagic	13 (0.3)	9 (0.2)	1.20 (0.50–2.91)	0.68
Type uncertain	0	1 (<0.1)	—	0.32

Mauri L. N Engl J Med 2014;371:2155-66.

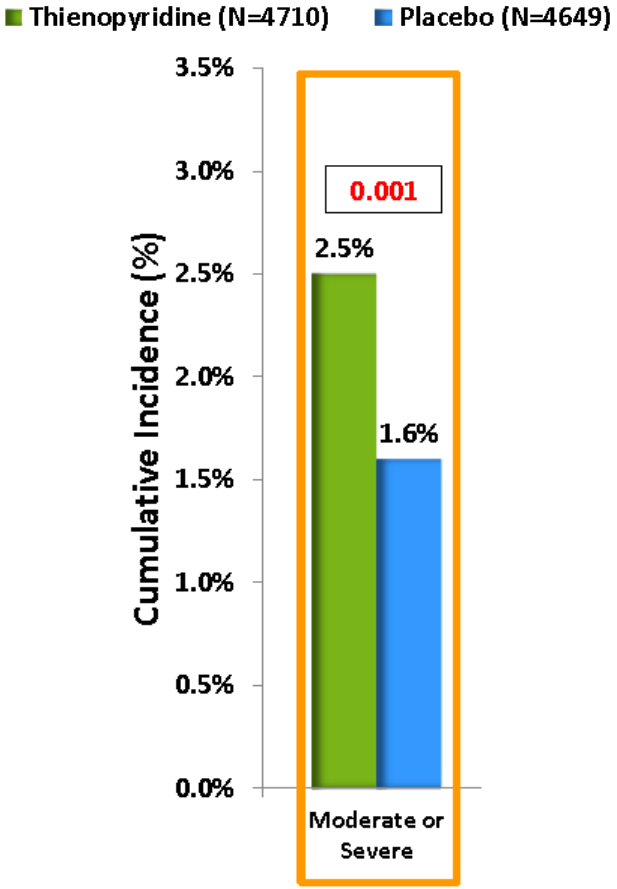
DAPT : extended DAPT worked in MI and non-MI



Mauri L. N Engl J Med 2014;371:2155-66.

DAPT : Safety profile

co-1° EP: Moderate or severe bleeding



All-Cause Mortality

12-30 Months	Thienopyridine N=5020	Placebo N=4941	P-Value	Absolute Difference
All-Cause Mortality	98 (2.0%)	74 (1.5%)	0.052	24 (0.5%)
Cardiac	45 (0.9%)	47 (1.0%)	0.98	-2 (-0.1%)
Vascular	5 (0.1%)	5 (0.1%)	0.98	0 (-)
Non-Cardiovascular	48 (1.0%)	22 (0.5%)	0.002	26 (0.5%)

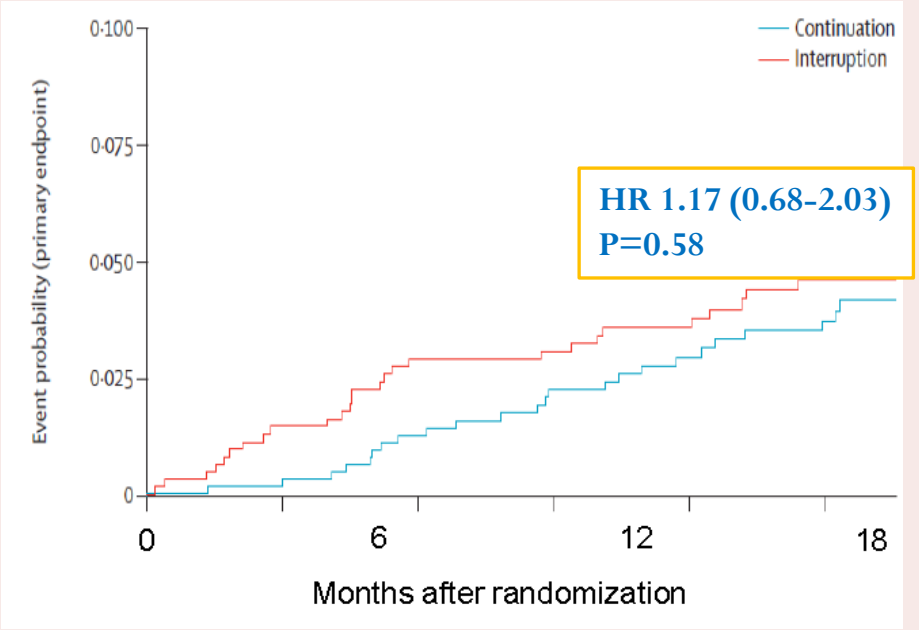
Mortality data in additional blinded adjudication and meta-analysis

Non-Cardiovascular Deaths, 12-33 Months			
Relatedness for Deaths*	Thienopyridine N=5020	Placebo N=4941	P-value
Bleeding-Related Death	11 (0.22%)	3 (0.06%)	0.057
Trauma-Related Death	9 (0.18%)	2 (0.04%)	0.07
Cancer-Related Death	31 (0.62%)	14 (0.28%)	0.02

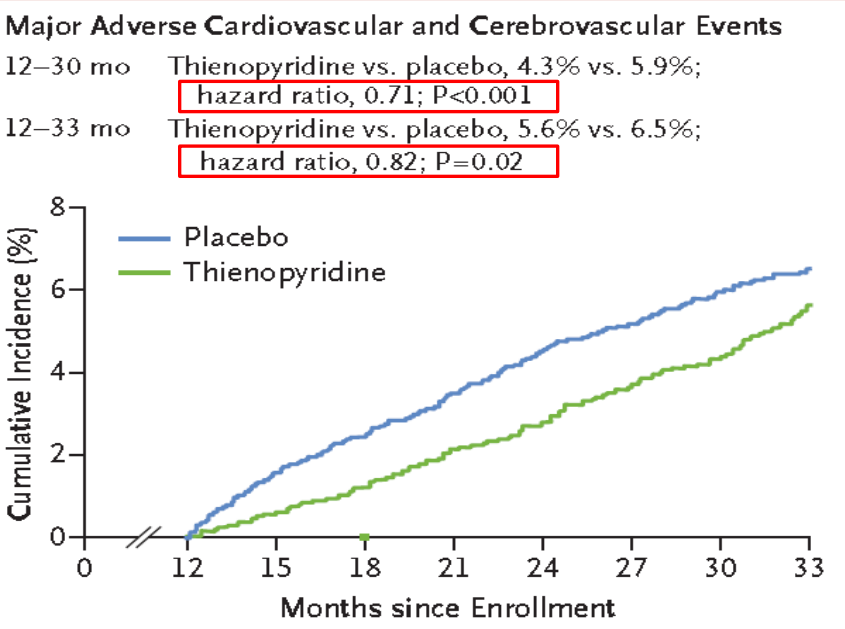
Mauri L. N Engl J Med 2014;371:2155-66.

Is longer better?

ARCTIC-INTERRUPTION



DAPT



MACCE

Bleeding

Major or minor bleeding (STEEPLE definition)
1.9% vs. 0.5%, p=0.04

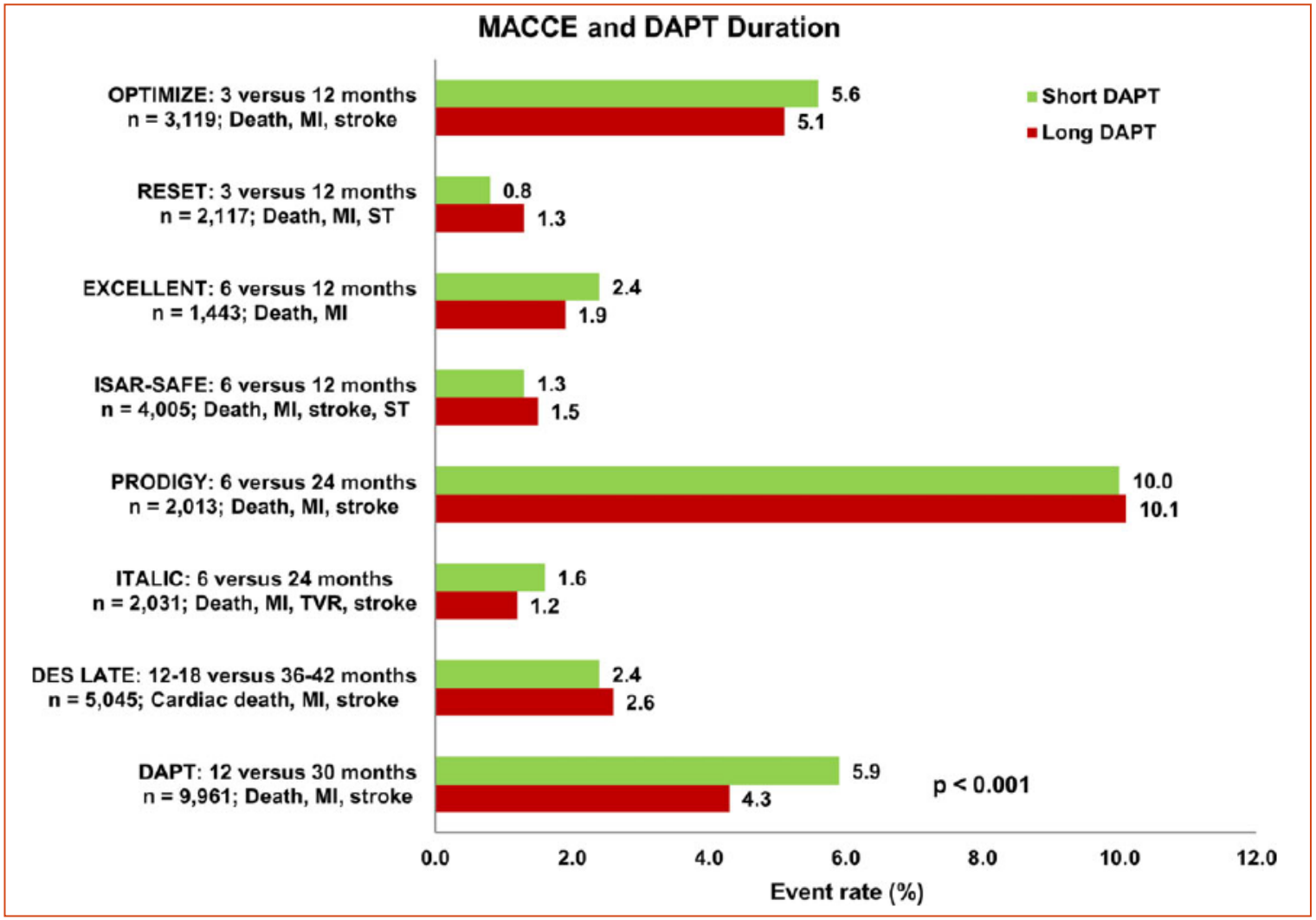
Moderate or severe bleeding (GUSTO definition)
2.5% vs. 1.6%, p=0.001

Collet JP. Lancet. 2014;384:1577-85.
Mauri L. N Engl J Med 2014;371:2155-66.

How about in meta-analysis …

Longer vs Shorter DAPT in DES

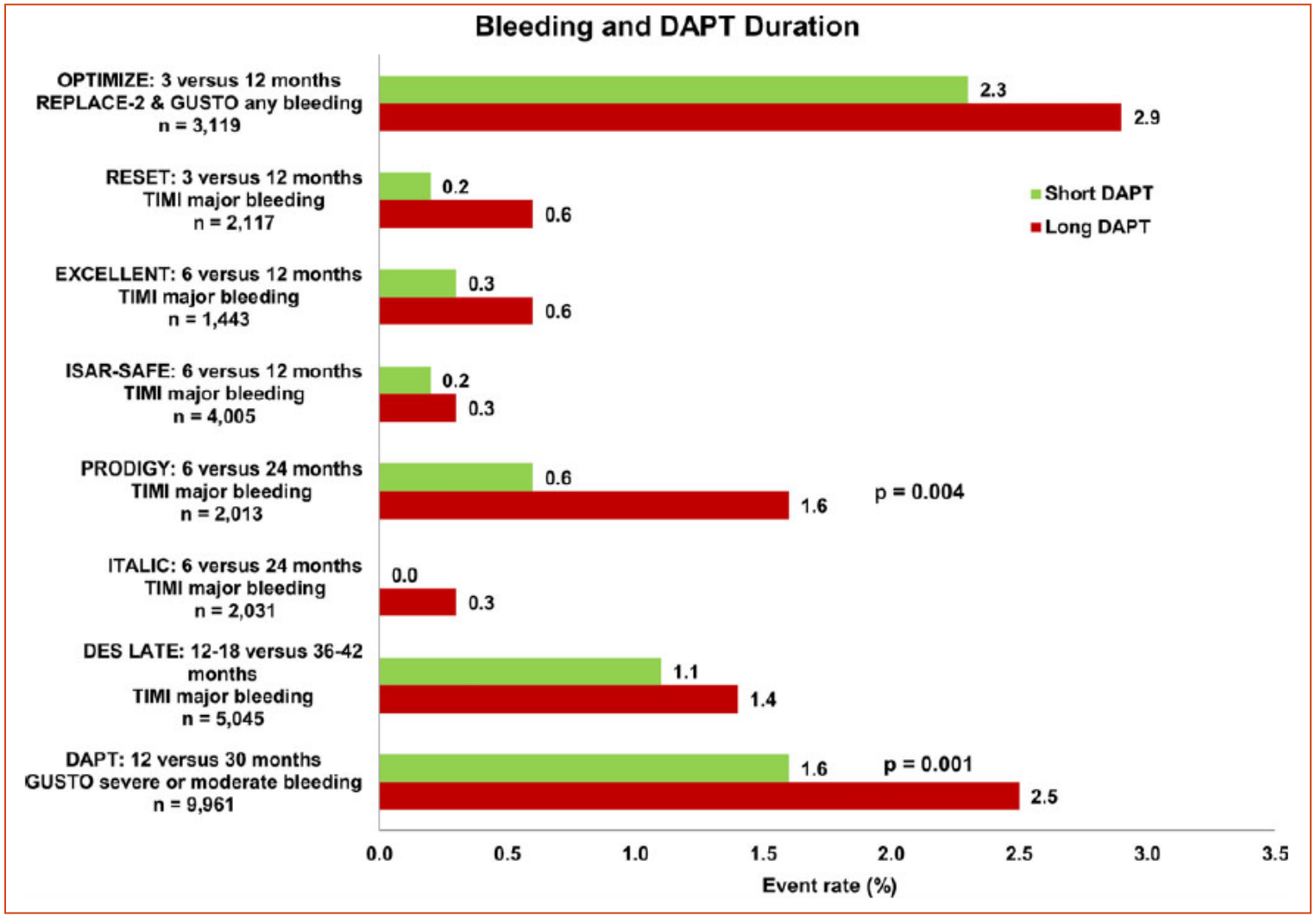
- From 9 trials including RESET: MACE side



Binder RK Eur Heart J. 2015;36:1207-11.

Longer vs Shorter DAPT in DES

- From 9 trials including RESET: MACE side



Binder RK Eur Heart J. 2015;36:1207-11.

DAPT duration: ischemic side and bleeding side

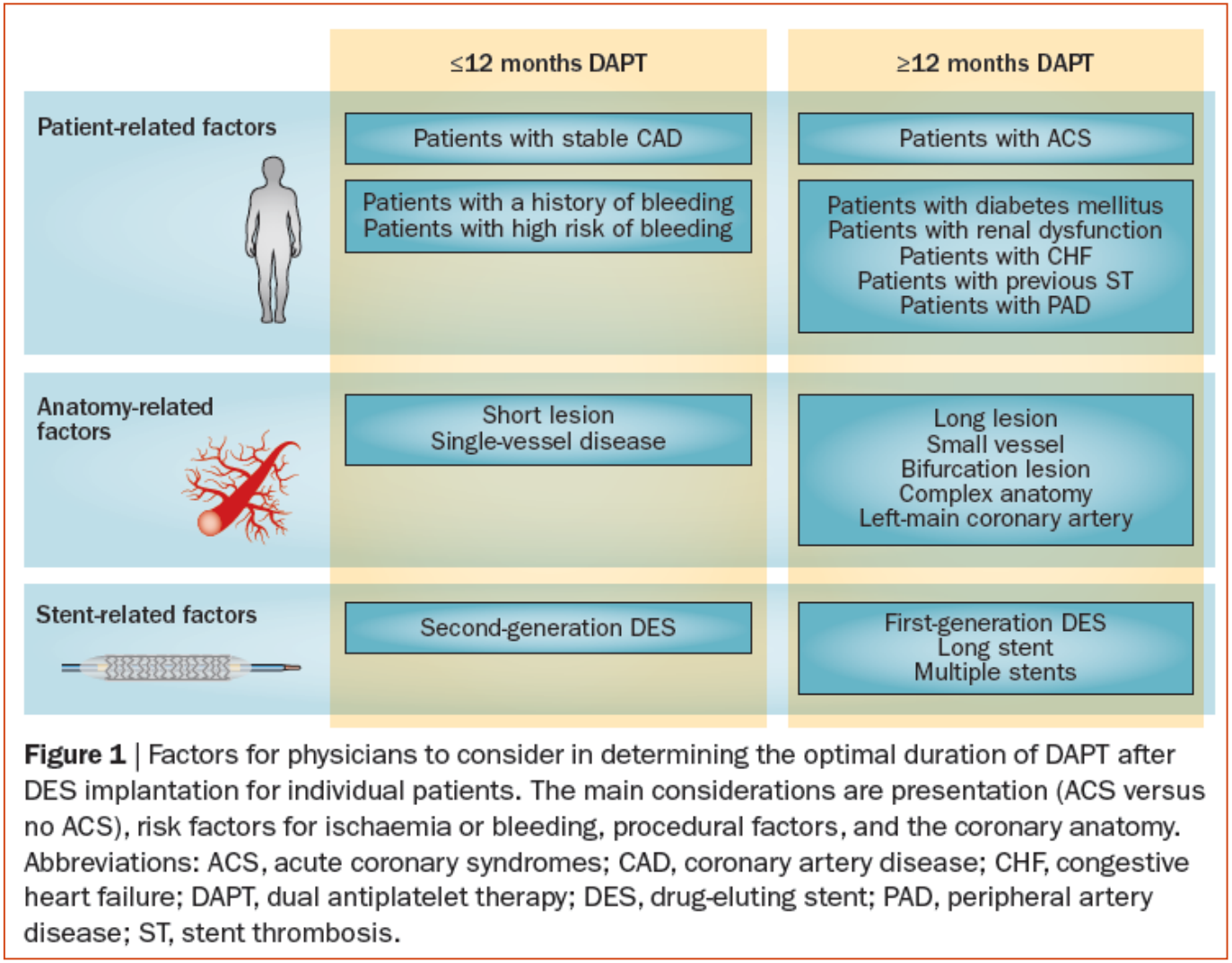
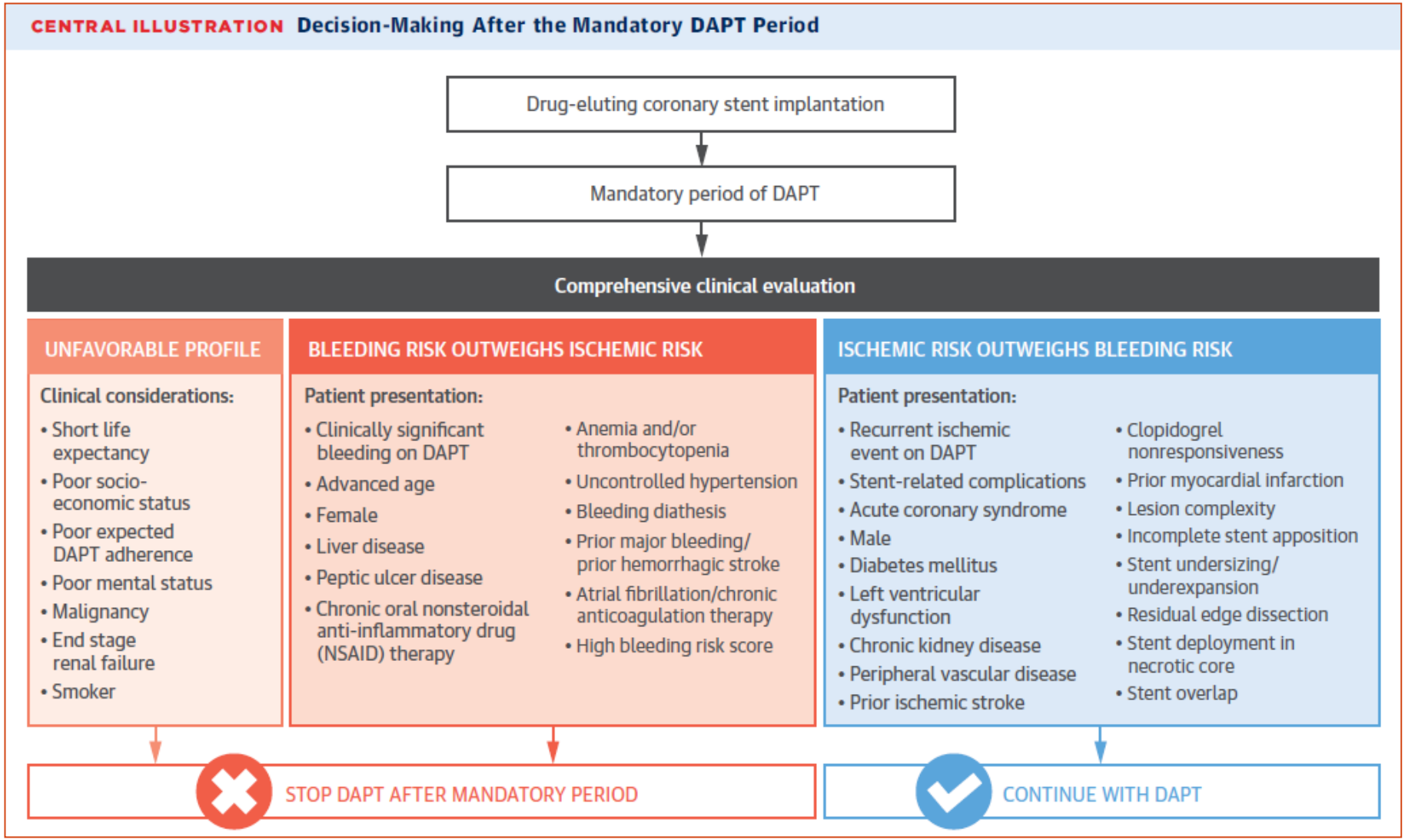


Figure 1 | Factors for physicians to consider in determining the optimal duration of DAPT after DES implantation for individual patients. The main considerations are presentation (ACS versus no ACS), risk factors for ischaemia or bleeding, procedural factors, and the coronary anatomy. Abbreviations: ACS, acute coronary syndromes; CAD, coronary artery disease; CHF, congestive heart failure; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; PAD, peripheral artery disease; ST, stent thrombosis.

Nat Rev Cardiol. 2015;12:445-6.

DAPT duration: ischemic side and bleeding side



J Am Coll Cardiol. 2015;66:832-47.

DAPT duration: risk factors for bleeding

- Prolonged DAPT benefit was shed off with bleeding

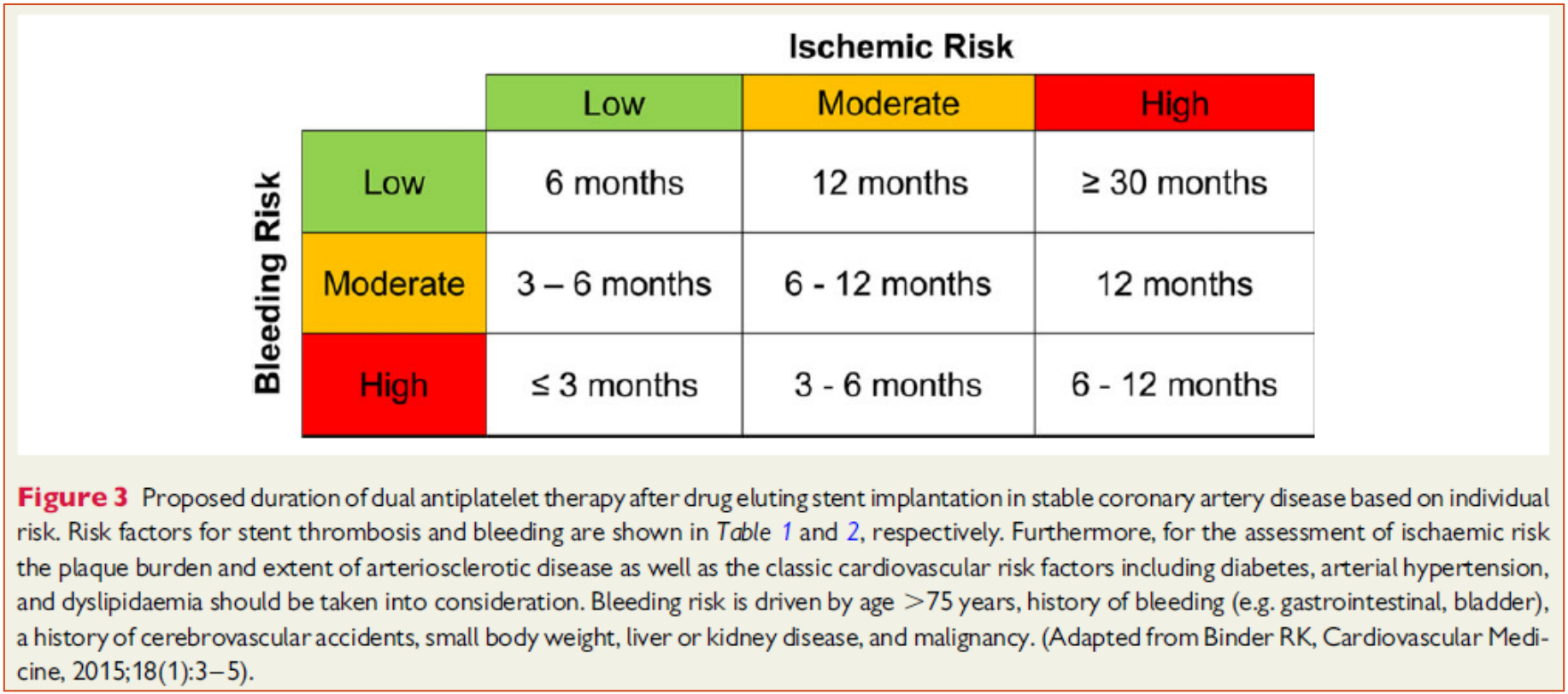
Table 2 Long-term risk factors for bleeding after percutaneous coronary intervention

Procedural factors	Patient characteristics	Pharmacological factors
Short-term risk factors:	Age	Prolonged dual antiplatelet therapy
Femoral access,	History of bleeding	Concomitant use of oral anticoagulation
Large sheath size	Low body weight	
No vascular closure device	Acute coronary syndrome	
Long-term risk factors:	Thrombocytopenia	
Unknown	Gastro-intestinal disease	
	Impaired kidney function	
	Liver disease	
	Cerebrovascular accident	
	Malignancy	

Binder RK. Eur Heart J 2015;36:1207-11.

DAPT duration: risk factors for bleeding

- No 'ONE-SIZE-FITS-ALL': table for stable coronary artery disease



Bleeding Risk \ Ischemic Risk	Low	Moderate	High
Low	6 months	12 months	≥ 30 months
Moderate	3 – 6 months	6 - 12 months	12 months
High	≤ 3 months	3 - 6 months	6 - 12 months

Figure 3 Proposed duration of dual antiplatelet therapy after drug eluting stent implantation in stable coronary artery disease based on individual risk. Risk factors for stent thrombosis and bleeding are shown in *Table 1* and *2*, respectively. Furthermore, for the assessment of ischaemic risk the plaque burden and extent of arteriosclerotic disease as well as the classic cardiovascular risk factors including diabetes, arterial hypertension, and dyslipidaemia should be taken into consideration. Bleeding risk is driven by age >75 years, history of bleeding (e.g. gastrointestinal, bladder), a history of cerebrovascular accidents, small body weight, liver or kidney disease, and malignancy. (Adapted from Binder RK, Cardiovascular Medicine, 2015;18(1):3–5).

Binder RK. Eur Heart J 2015;36:1207-11.

DAPT duration: severity of CAD

- Stable CAD
  - The 1st generation of DES: Taxus, especially Cypher
    - > 1 year of DAPT
  - Newer generation of DES
    - 6 months, possible in 3 months

- Acute coronary syndrome
  - At least 1 year of DAPT, irrespective of treatment modality
  - Possible more than 1 year of DAPT (reduced dose of potent antiplatelet agents)

- Rebound after dual antiplatelet therapy cessation
  - Striking increment of event within the 1st 3 months of DAPT cessation in DAPT
    - Unmasked incomplete stent endothelialization, or vulnerable plaque
    - True rebound effect with increased platelet agreeability after DAPT withdrawal

Binder RK. Eur Heart J 2015;36:1207-11.