How to Optimize Antiplatelet Strategy in CHIP Patients

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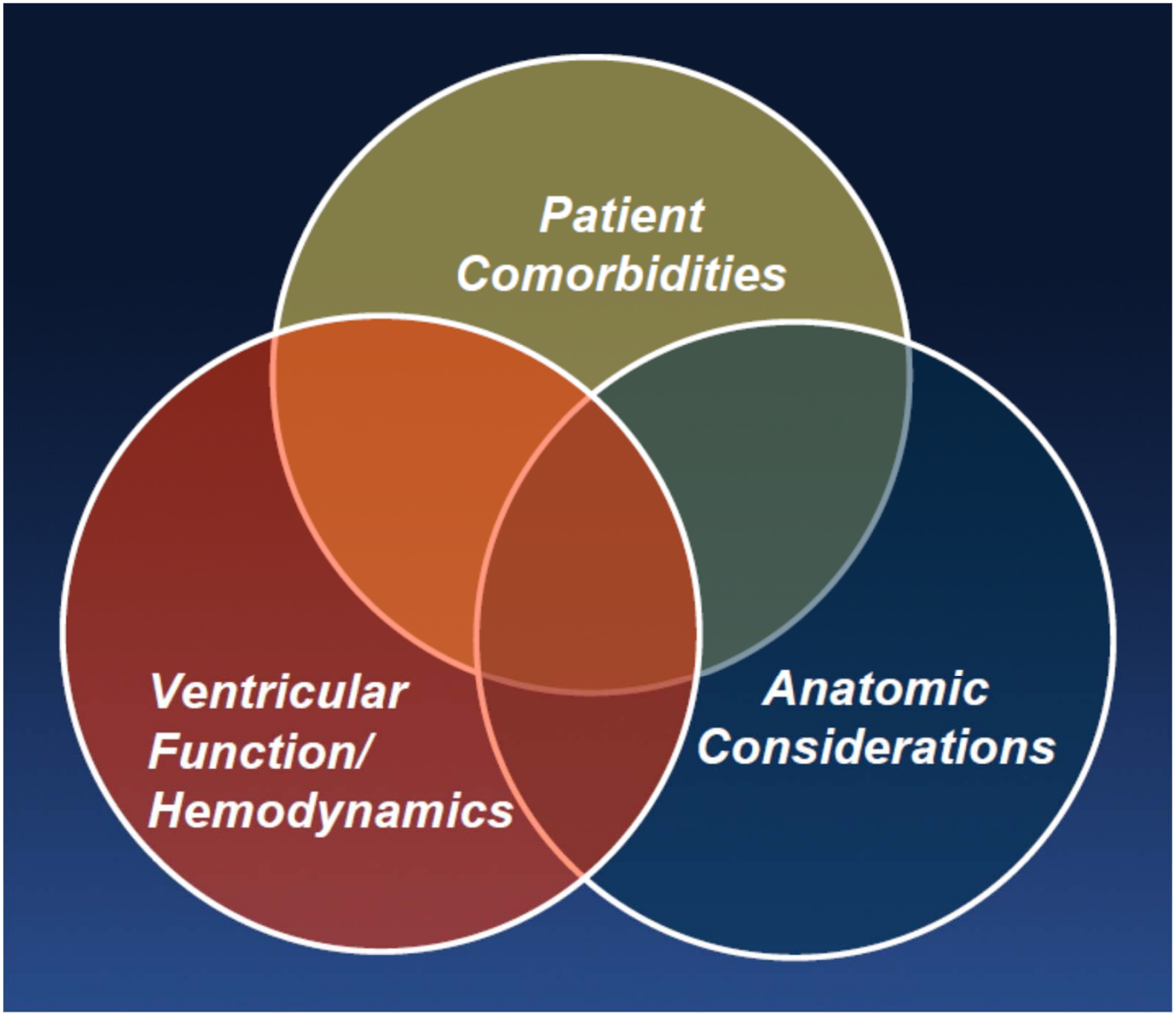
Complex Higher-risk(and Indicated) Patients (CHIP)



Kirtane AJ, Circulation 2016

What is CHIP ?

Example of CHIP Procedures

Solutions for high-risk patients

So, CHIP is rather a cluster of patients with complex coronary anatomy including high-risk CAD and/or structural heart disease.

→ Therefore, the focus of treatment is on complete revascularization or correction of the CAD (or SHD).

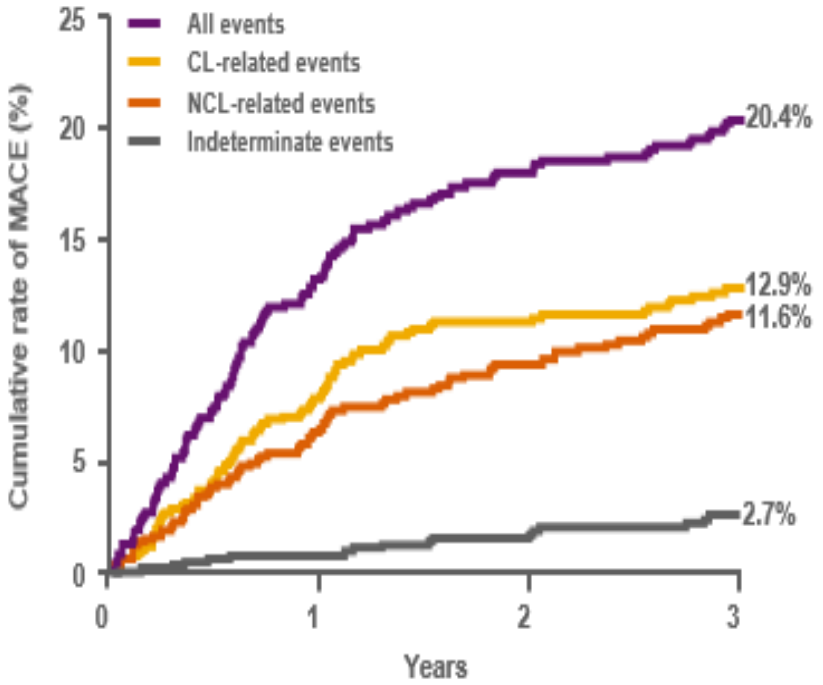
Antiplatelet therapy in this setting remains itself as having an adjunctive role (which is no different from conventional stable IHD in the guidelines)

- Heart transplantation or left-ventricular assist devices as a bridge to transplantation or destination therapy for appropriate candidates

UCLA-Health CHIP Program for Patients (Flyers)

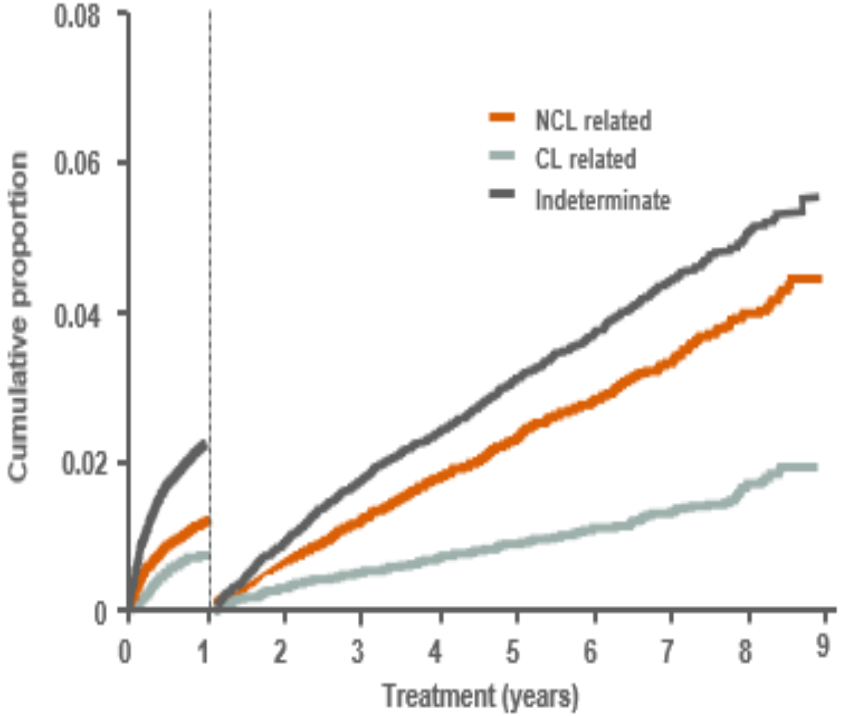
RWE highlights the long-term risk of subsequent atherothrombotic events that are distinct from previously stented lesions

The **PROSPECT** study explored the occurrence of MACE, following PCI in 697 ACS patients over a median follow-up of 3.4 years[1]



The rate of recurrent events was similar in "culprit" and "non-culprit" lesions

PRECLUDE: A retrospective study of SWEDEHEART registry data analysed the characteristics of recurrent MIs in 41,789 MI patients with a defined culprit lesion over 8 years follow-up[2]

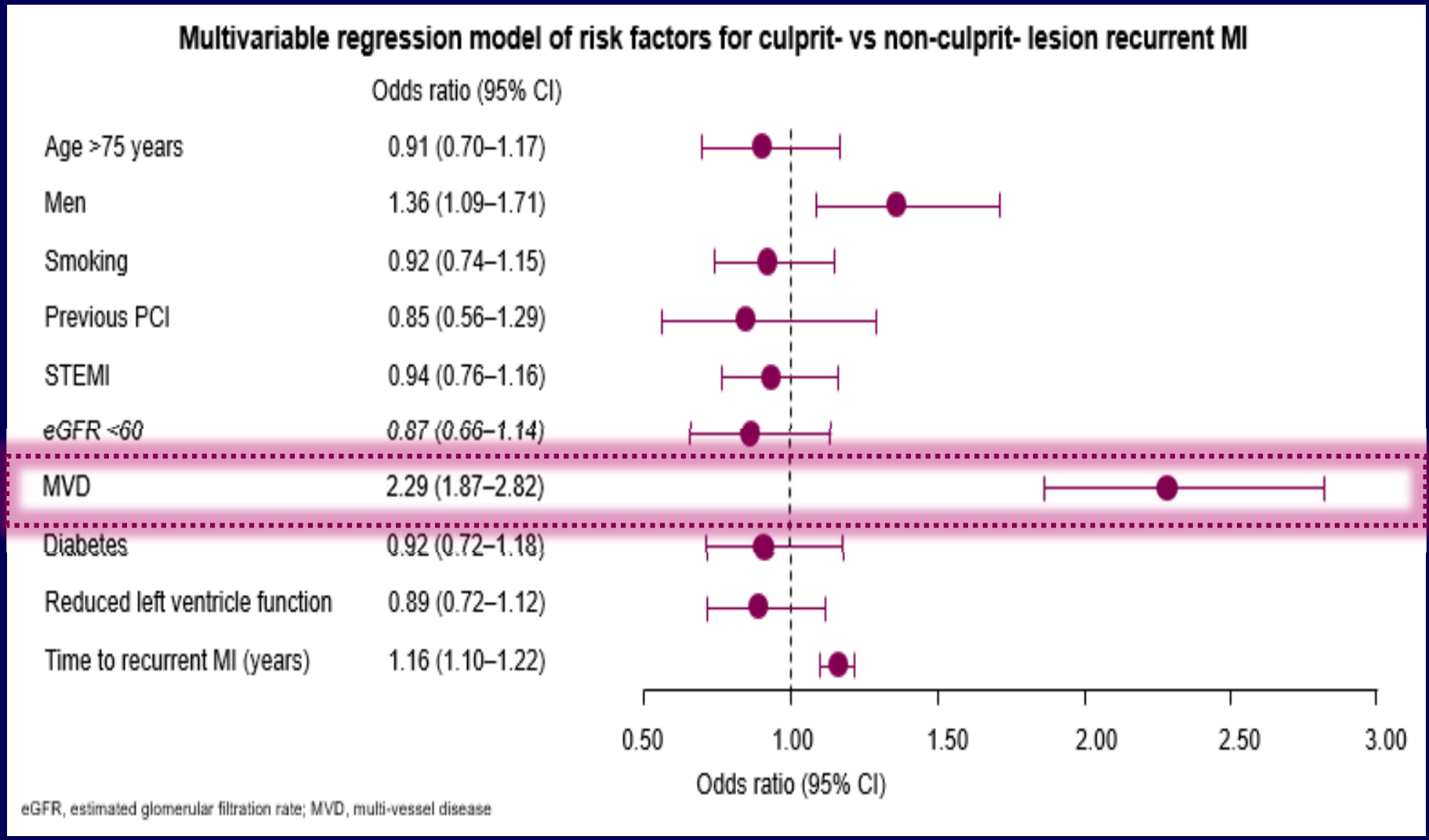


The rate of recurrent events was twice as high in 'non-culprit' lesions than in 'culprit' lesions

CL, culprit lesion; NCL, non-culprit lesion

1. Stone GW et al. N Engl J Med 2011;364:226–235; 2. Varenhorst C et al. Presented at AHA 2016, CH.AOS.730 oral sessions

MVD, time to recurrent MI and male sex were associated with a higher risk of recurrent MI at a non-culprit lesion than a culprit lesion (PRECLUDE : SWEDENHEART registry)



CL, culprit lesion; NCL, non-culprit lesion

Varenhorst C et al. J Am Heart Assoc 2018;7:e007174

DAPT prolongation significantly benefits patients with complex PCI but not those Non-Complex PCI in terms of coronary thrombotic events

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Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI

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ABSTRACT

BACKGROUND Optimal upfront dual antiplatelet therapy (DAPT) duration after complex percutaneous coronary intervention (PCI) with drug-eluting stents (DES) remains unclear.

OBJECTIVES This study investigated the efficacy and safety of long-term (≥12 months) versus short-term (3 or 6 months) DAPT with aspirin and clopidogrel according to PCI complexity.

METHODS The authors pooled patient-level data from 6 randomized controlled trials investigating DAPT durations after PCI. Complex PCI was defined as having at least 1 of the following features: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion. The primary efficacy endpoint was major adverse cardiac events (MACE), defined as the composite of cardiac death, myocardial infarction, or stent thrombosis. The primary safety endpoint was major bleeding. Intention-to-treat was the primary analytic approach.

RESULTS Of 9,577 patients included in the pooled dataset for whom procedural variables were available, 1,680 (17.5%) underwent complex PCI. Overall, 85% of patients received new-generation DES. At a median follow-up time of 392 days (interquartile range: 366 to 710 days), patients who underwent complex PCI had a higher risk of MACE (adjusted hazard ratio [HR]: 1.98; 95% confidence interval [CI]: 1.50 to 2.60; $p < 0.0001$). Compared with short-term DAPT, long-term DAPT yielded significant reductions in MACE in the complex PCI group (adjusted HR: 0.56; 95% CI: 0.35 to 0.89) versus the noncomplex PCI group (adjusted HR: 1.01; 95% CI: 0.75 to 1.35; $p_{interaction} = 0.01$). The magnitude of the benefit with long-term DAPT was progressively greater per increase in procedural complexity. Long-term DAPT was associated with increased risk for major bleeding, which was similar between groups ($p_{interaction} = 0.96$). Results were consistent by per-treatment landmark analysis.

CONCLUSIONS Alongside other established clinical risk factors, procedural complexity is an important parameter to take into account in tailoring upfront duration of DAPT. (J Am Coll Cardiol 2016;68:1851–64)

* Giustino et al -J Am CollCardiol2016;68:1851–64

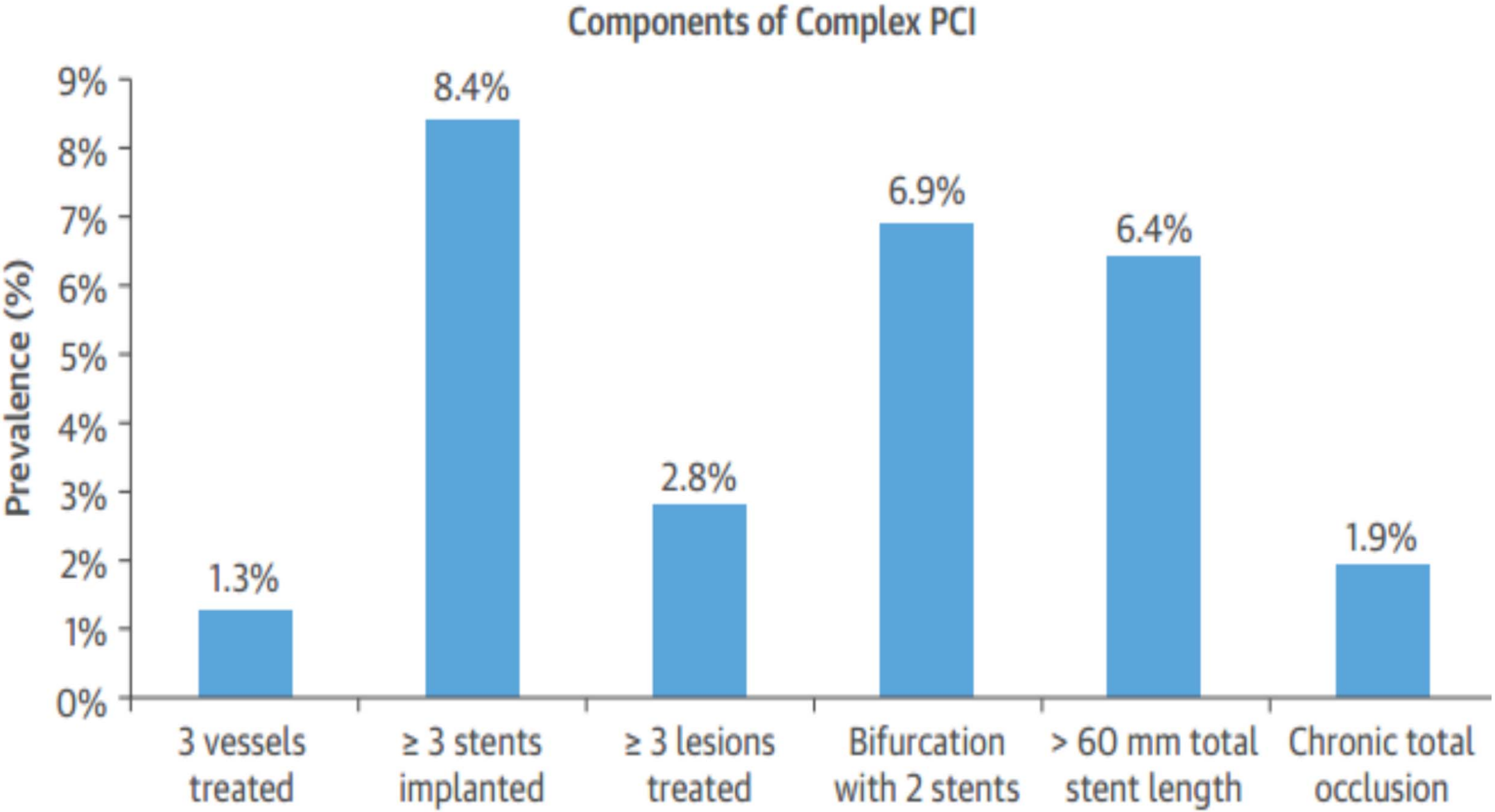
Meta analysis of 6 RCTs with complex PCI patients

Included RCTs

Study	N	Primary endpoint	Design	Follow-up	DAPT Duration (Months)	Primary Endpoint Results
RESET	3 months (N=1,059) 12 months (N=1,058)	Cardiac death/MI/ST/TVR/ major bleeding	Non-inferiority	1 year	3 vs.12	Non-inferiority demonstrated
EXCELLENT	6 months (N=722) 12 months (N=721)	Cardiac death/MI/ischemia-driven TVR	Non-inferiority	1 year	6 vs. 12	Non-inferiority demonstrated
PRODIGY	6 months (N=751) 24 months (N=750)	Death/MI/CVA	Superiority	2 years	6 vs. 24	Superiority of 24-month DAPT not demonstrated
OPTIMIZE	3 months (N=1,563) 12 months (N=1,556)	Death/MI/CVA/major bleeding	Non-inferiority	1 year	3 vs. 12	Non-inferiority demonstrated
SECURITY	6 months (N=682) 12 months (N= 717)	Cardiac death/MI/CVA/ST/major bleeding	Non-inferiority	1 year	6 vs. 12	Non-inferiority demonstrated
ITALIC PLUS	6 months (N=953) 24 months (N=941)	Death/MI/uTVR/CVA /major bleeding	Non-inferiority	2 years	6 vs. 24	Non-inferiority demonstrated

Giustino et al - J Am Coll Cardiol 2016;68:1851–64

Prevalence and Overlap of Complex PCI Components



DAPT prolongation significantly benefits patients with complex PCI but not those non-complex PCI in terms of coronary thrombotic events

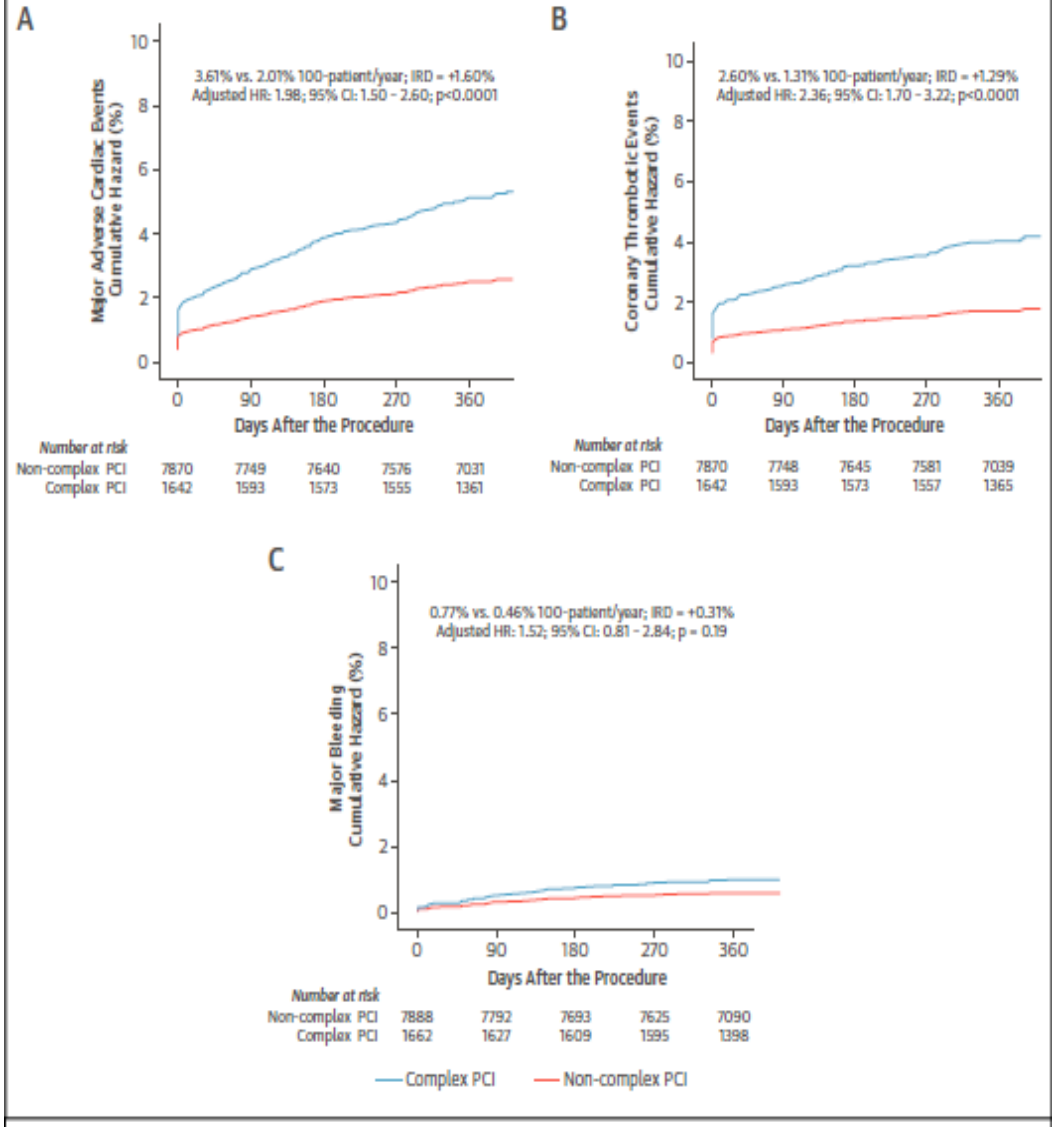
TABLE 1 Baseline Characteristics in All Randomized Patients According to PCI Complexity

	Complex PCI (n = 1,680)	Noncomplex PCI (n = 7,897)	p Value
Age, yrs	63.6 ± 10.8	63.4 ± 10.5	0.36
Male	1,154 (68.7)	5,345 (67.7)	0.16
Clinical history			
Hypertension	1,252 (74.6)	5,914 (75.1)	0.74
Diabetes mellitus	602 (35.8)	2,430 (30.8)	0.006
Dyslipidemia	1,091 (65.5)	4,874 (62.6)	0.59
Current smoking	391 (26.5)	1,721 (26.1)	0.90
Prior MI	344 (20.5)	1,619 (20.6)	0.88
Prior PCI	221 (13.2)	1,158 (14.7)	0.44
Prior coronary artery bypass graft	82 (4.9)	444 (5.6)	0.65
Prior stroke	68 (5.4)	192 (3.5)	0.31
Clinical presentation			0.37
Stable CAD	884 (52.6)	4,503 (57.0)	
ACS*	796 (47.4)	3,393 (43.0)	
High-risk ACS†	300 (17.9)	1,271 (16.1)	
Angiographic and procedural characteristics			
Number of diseased vessels/patient	1.9 ± 0.8	1.5 ± 0.7	–
Number of vessels stented/patient‡	1.5 ± 0.7	1.2 ± 0.4	–
Number of lesions stented/patient‡	1.8 ± 0.8	1.2 ± 0.4	–
Number of stents implanted/patient‡	2.5 ± 1.2	1.3 ± 0.5	–
Any bifurcation treated with 2 stents‡	658 (16.2)	–	–
Any chronic total occlusion treated‡	182 (2.7)	–	–
Target vessels			
Left main	49 (5.1)	106 (1.8)	<0.0001
Left anterior descending artery	1,119 (78.6)	3,683 (59.4)	<0.0001
Left circumflex artery	636 (53.5)	1,639 (27.5)	<0.0001
Right coronary artery	618 (54.6)	1,974 (32.7)	<0.0001
Type of DES implanted§			<0.0001
Early-generation DES	243 (14.9)	942 (12.1)	
New-generation DES	1,386 (85.1)	6,874 (87.9)	
Randomization			0.52
Longer DAPT	826 (49.2)	3,951 (50.0)	
Shorter DAPT	854 (50.8)	3,946 (50.0)	

Values are mean ± SD or n (%). *Includes unstable angina, non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction. †Includes non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction. ‡Variable included in the Complex PCI definition, reported for descriptive purposes. §Old-generation DES include sirolimus- and paclitaxel-eluting stents; new-generation DES include everolimus-, zotarolimus-, and biolimus-eluting stents.

ACS = acute coronary syndrome(s); CAD = coronary artery disease; DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); MI = myocardial infarction; PCI = percutaneous coronary intervention.

FIGURE 2 Effect of Procedural Complexity on Ischemic and Bleeding Outcomes



Cumulative hazard curves for major adverse cardiac events (**A**), coronary thrombotic events (**B**), and major bleeding (**C**). Incidence rates are expressed as 100 patient-years of follow-up. CI = confidence interval; HR = hazard ratio; IRD = incidence rate difference; PCI = percutaneous coronary intervention.

* Giustino et al -J Am CollCardiol2016;68:1851–64

DAPT prolongation significantly benefits patients with complex PCI but not those non-complex PCI in terms of coronary thrombotic events

Complex PCI group has more event rate than non-complex PCI group in meta-analyses of DES trials using aspirin and clopidogrel only.

➔ The solution ……

1) **Continue the P2Y12 inhibitor beyond 1 year.**
2) **May consider using potent P2Y12 inhibitors as long as indicated.**

Days after the procedure

Increase in PCI complexity

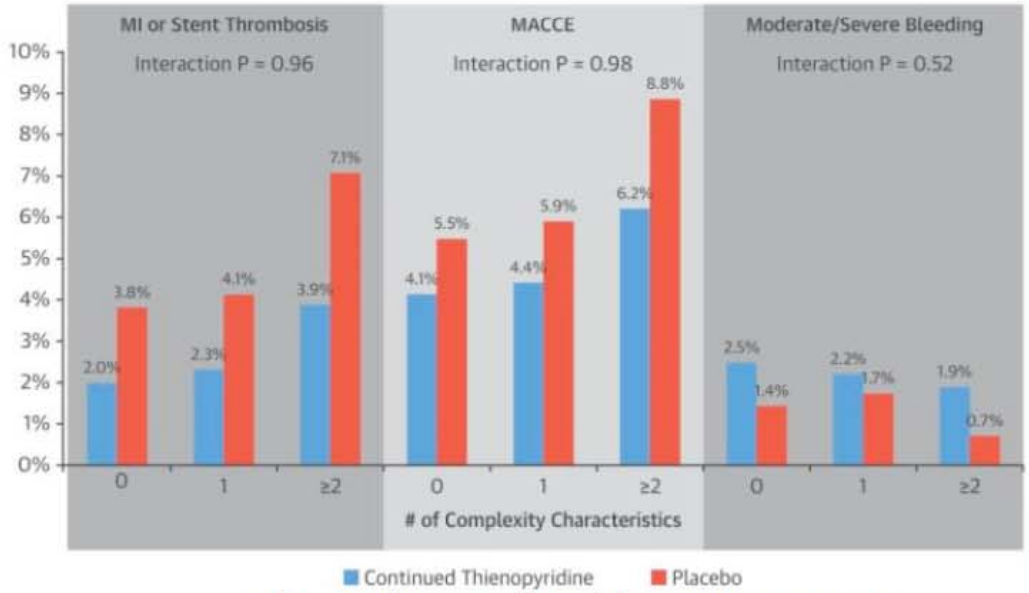
Antiplatelet Issues on PCI for Complex Coronary Lesions

Association between Complex Lesion and Subsequent Events

- Attenuated after first year post PCI

- **Risk of Ischemic Events is High in the First Year after Complex PCI**

	From 0-12 Months		From 12-30 Months	
Predictors	Odds Ratio	P Value	Hazard Ratio	P Value
Total stent length > 60 mm	2.07 [1.63, 2.63]	<0.001	1.41 [0.93, 2.15]	0.11
≥ 3 Stents implanted	1.68 [1.37, 2.05]	<0.001	1.17 [0.82, 1.66]	0.38
≥ 3 Lesions treated	1.84 [1.41, 2.40]	<0.001	1.10 [0.67, 1.82]	0.70
Bifurcation lesion with SB ≥ 2.5 mm and ≥ 2 stents	1.60 [1.13, 2.27]	0.01	1.36 [0.80, 2.32]	0.26
Chronic total occlusion	1.06 [0.70, 1.60]	0.78	0.56 [0.25, 1.24]	0.15



Yeh R. et al. J Am Coll Cardiol. 2017;30:2213-2223

Among patients enrolled and randomized in the DAPT Study, we found that those undergoing PCI with more complex coronary artery target lesions had a higher rate of subsequent ischemic events, particularly within the first year after PCI, compared with patients without complex lesions. After the first year, this association was attenuated. Consistent with this observation, among patients reaching 1 year after PCI without a major ischemic or bleeding event, the magnitude of ischemic benefit associated with continuing thienopyridine for an additional 18 months was not greater among patients with complex coronary lesion characteristics than those without. Independent of anatomical complexity of the index lesion, those with DAPT scores ≥2 derived greater ischemic reductions with a numerically lesser

Courtesy of Park KW

Lesion Complexity and Outcomes of Extended DAPT After PCI

11,554 pts from the DAPT Study who survived event-free for 1 year were randomized to aspirin plus thienopyridine or placebo for 18 months.

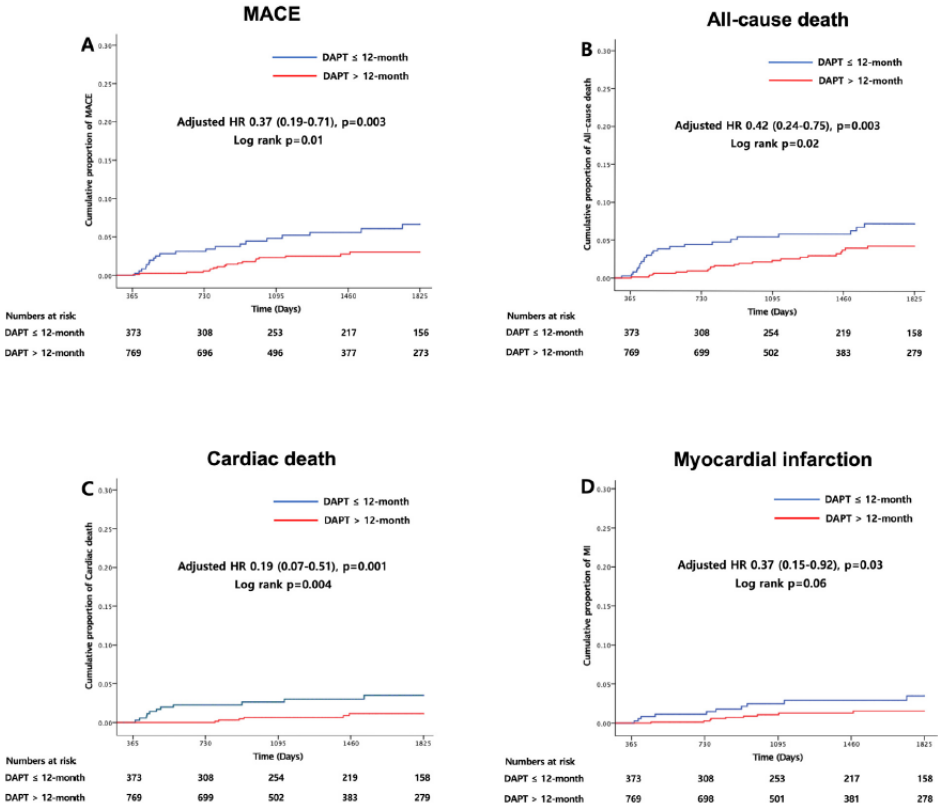
- **Regardless of lesion complexity, patients had similar rates of MI or stent thrombosis between 12 and 30 months**
- **The relative reduction of MI/stent thrombosis and increase in moderate/severe bleeding linked with prolonged DAPT was similar for those with or without complex index lesions**
- **Those with complex lesions and DAPT scores ≥ 2 had greater absolute reductions in MI/stent thrombosis over time with continued thienopyridine treatment vs pts with lower scores**

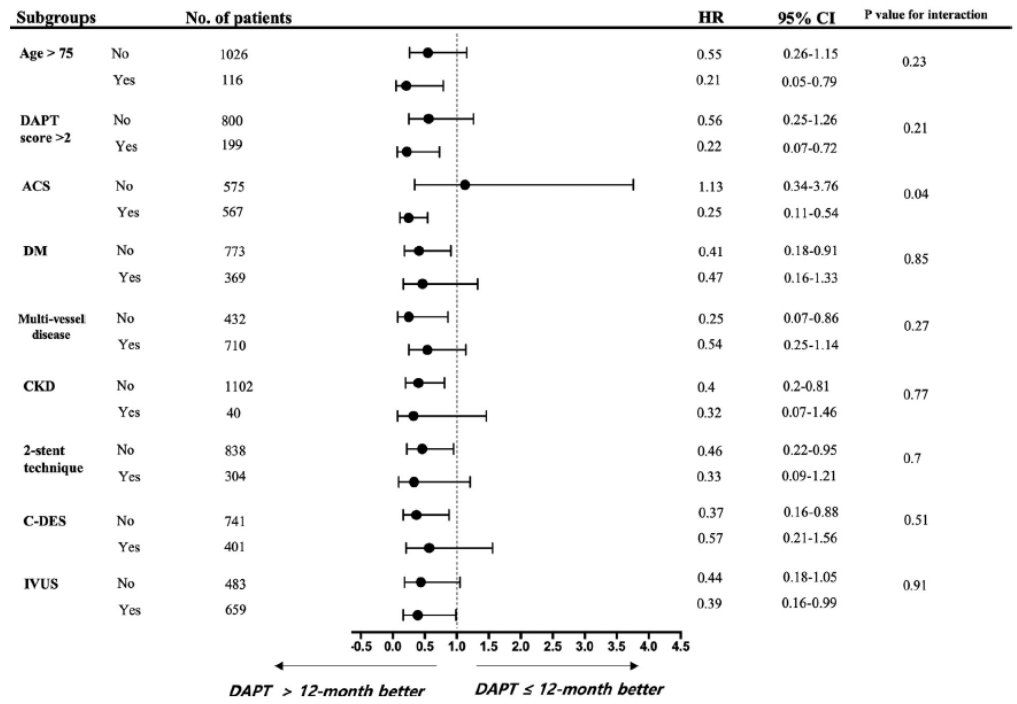
Implications: **The longer a patient survives after PCI without incident, the less relevant the complexity of their index lesion becomes to their ischemic event risk over time.**

Yeh RW, et al. *J Am Coll Cardiol.* 2017;70:2213-2223.

Antiplatelet Issues on PCI for Bifurcation Lesions

- Current PCI guideline for SIHD (2017) does not differentiate bifurcation lesion for specific treatment group, including antiplatelet therapy.
- Some studies focused on the duration of DAPT post PCI.
- In a study by Cho S et al, KOMATE/COBIS registries(N=1,142) shown better ischemic outcome with extended use of DAPT(>12 months) as compared with conventional DAPT(<12 months) in first generation DES(SES/PES), while it was not the case with later generation DES(ZES/EES/BES).





Cho S et al, AJC 2019

Antiplatelet Issues on PCI for CTO

- **Current PCI guideline for SIHD (2017) does not differentiate CTO for specific treatment group, including antiplatelet therapy.**
- **Potential complications by CTO-PCI advocates the use of clopidogrel as standard P2Y12 inhibitor (No studies conducted regarding different type of P2Y12 inhibitor use).**
- **Small number of studies focused on the duration of DAPT post CTO-PCI.**

Comparison of 512 patient underwent CTO-PCI who is event-free at 12-months according to DAPT duration (>12-Mo; 199 vs <12-Mo; 313) in SMC CTO Registry

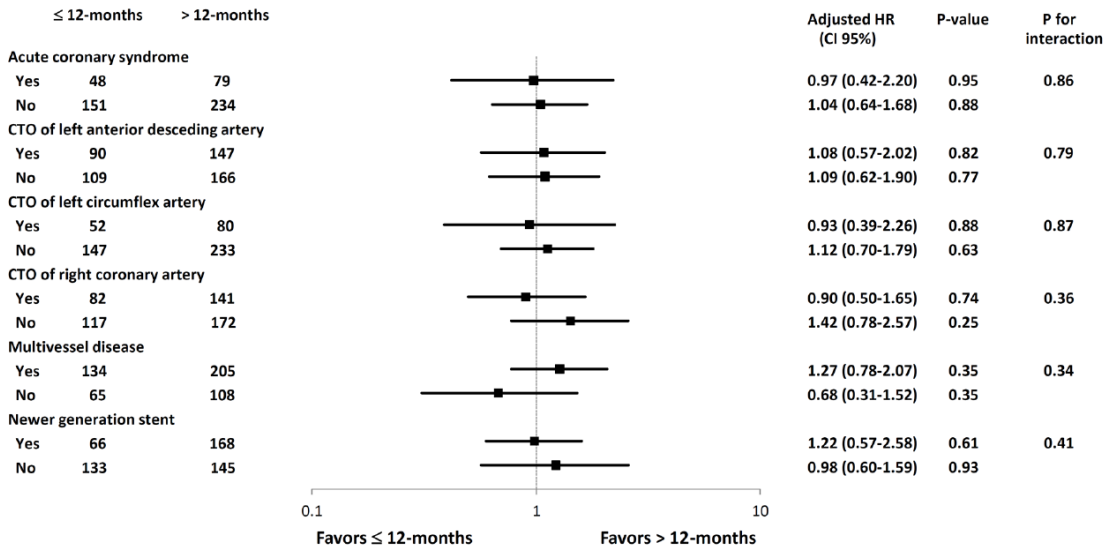
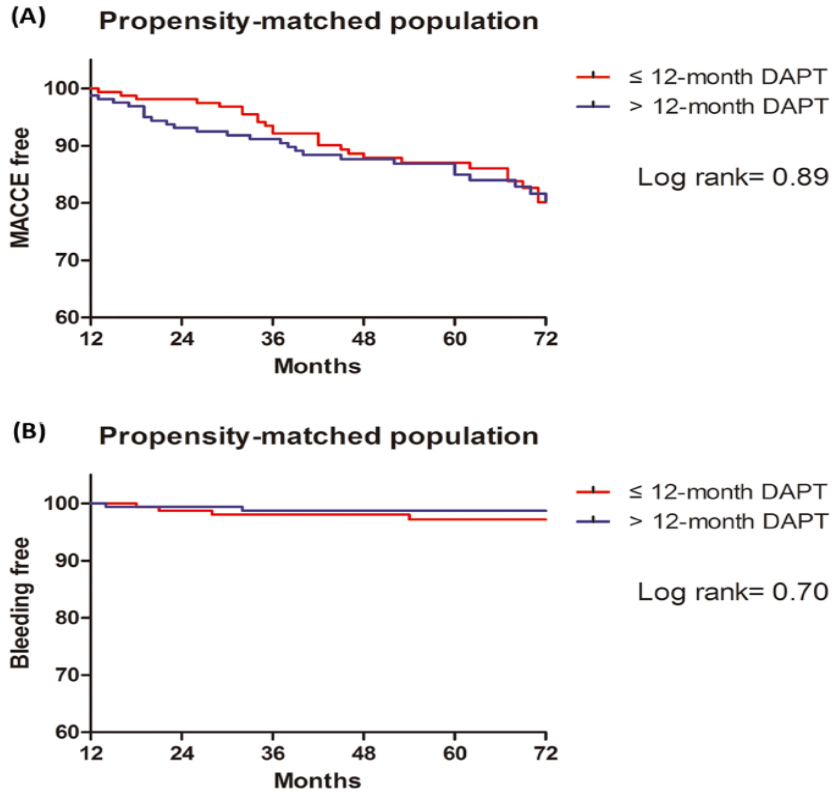


Fig 5. Comparison of MACCE in the subgroups. 95%CI, 95% confidence interval; HR, hazard ratio; CTO, chronic total occlusion.



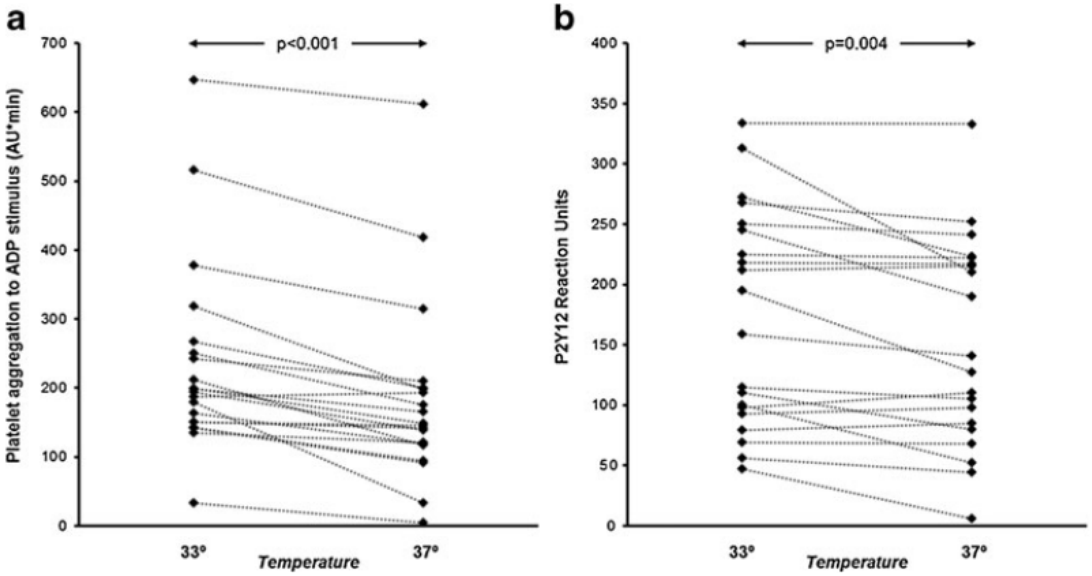
Lee SH et al, PLosOne 2017

Antiplatelet Issues on patients with AMI with cardiogenic shock with coma undergoing therapeutic hypothermia

- Even in the presence of coma, primary reperfusion for AMI(mostly STEMI) should not be delayed, as well as considering therapeutic hypothermia if deemed necessary.
- Hypothermia may be associated with impaired response to clopidogrel and greater risk of thrombotic complications after PCI.
- Small PD investigation shown that hypothermia was associated with reduced clopidogrel-mediated platelet inhibition with no impact on aspirin effects ➔ *May advocate the use of potent P2Y12 inhibitors(prasugrel or ticagrelor) in this setting.*

Impact of Mild Hypothermia on Platelet Responsiveness to Aspirin and Clopidogrel: an In Vitro Pharmacodynamic Investigation

José Luis Ferreiro · José Carlos Sánchez-Salado · Montserrat Gracida · Ana Lucrecia Marcano · Gerard Roura · Albert Ariza · Josep Gómez-Lara · Victoria Lorente · Rafael Romaguera · Sílvia Homs · Guillermo Sánchez-Elvira · Luis Teruel · Kristian Rivera · Silvia Gabriela Sosa · Joan Antoni Gómez-Hospital · Dominick J. Angiolillo · Ángel Cequier



Ferreiro et al, JCTR 2014

Antiplatelet Issues on patients with AMI with cardiogenic shock with coma undergoing therapeutic hypothermia

Recommendation of antithrombotic therapy for AMI with cardiogenic shock

Antithrombotic management

- Ticagrelor or prasugrel are favored over clopidogrel;
- Unfractionated heparin is favored over other anticoagulants;
- GPIs (mostly abciximab) can be considered selectively in the presence of a high thrombus burden and when bioavailability of orally administered P2Y12 inhibitors is uncertain;
- Cangrelor can be considered if absorption of orally administered P2Y12 inhibitors is uncertain;
- Gastrointestinal dysmotility and acute hepatic and kidney injury induce unpredictable alterations of antithrombotic drugs pharmacokinetics and pharmacodynamics;
- Targeted temperature management induces acquired platelet dysfunction and diminishes the bioavailability of orally administered drugs.

Marquis-Gravel G et al, CCI 2019

Spectrum of CHIP and its impact on antiplatelet therapy

Patient/Lesion Subsets	Techniques/Devices	Impact on Antiplatelet Therapy
Chronic total occlusions	Dual access and injections	Favors clopidogrel than prasugrel/ticagrelor(due to potential bleeding issues with more transfemoral approach, chances of vessel injury during CTO-PCI)
	Antegrade and retrograde techniques, including dissection/re-entry devices Specialty wires, microcatheters, devices for increasing guide/catheter support, externalization techniques	
Left main stenosis/ bifurcations	Single- and 2-stent strategies (both primary and for provisional/bailout use) Intravascular imaging	Favors clopidogrel as SOC
Calcific disease	Rotational/orbital atherectomy	Favors clopidogrel as SOC(esp. with atherectomy procedure anticipated)
	Intravascular imaging	
Multivessel disease	Coronary physiological studies (eg, fractional flow reserve) Intravascular imaging	Favors clopidogrel as SOC

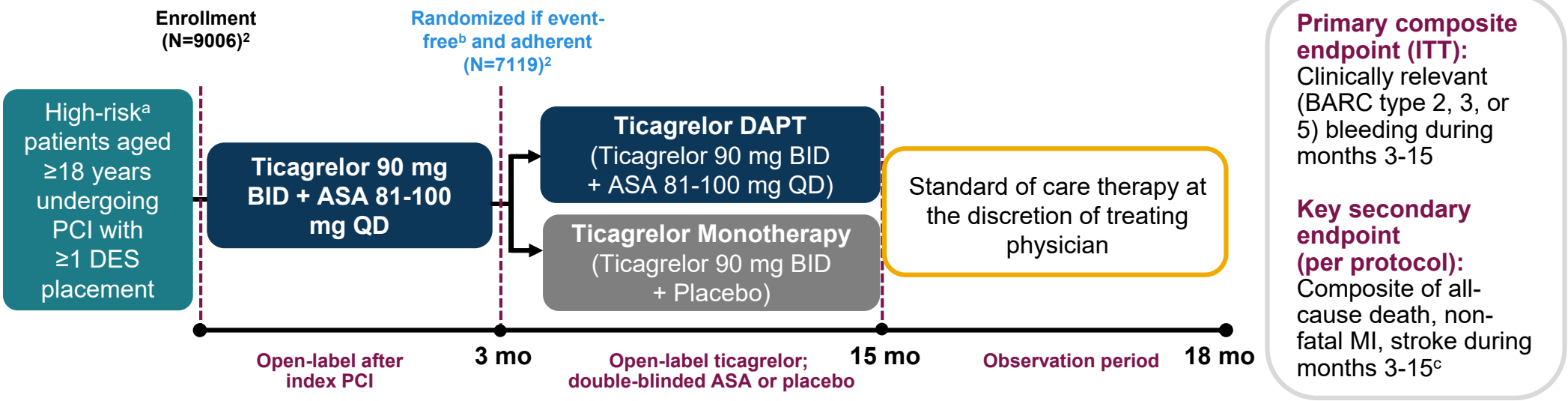
Kirtane AJ, Circulation 2016

		Impact on Antiplatelet Therapy
Poor hemodynamic status/ventricular function coexisting with complex anatomy	Left/right ventricular percutaneously implanted support devices	Proper hemodynamic support → antiplatelet therapy as needed according to clinical presentation(ACS or non-ACS) Cardiac arrest → prefer more potent antiplatelet agent to overcome drug absorption issues
	Intra-aortic balloon counterpulsation	
	Extracorporeal membrane oxygenation	
	Large-vessel access/closure management	
	Transradial expertise (when both femoral arteries are used)	
	Alternative access considerations (axillary, transcaval)	
Stent underexpansion/ restenosis	Intravascular imaging	Antiplatelet therapy as needed
	Aggressive noncompliant and plaque-modification balloons	
	Atherectomy (laser, rotational)	
	Vascular brachytherapy	
Complication management	Echocardiography-guided pericardiocentesis	Favors clopidogrel(to avoid bleeding complication issues)
	Covered stents, coils, beads	
	Snares/snaring techniques	
	Dual guide techniques	
	Dissection/re-entry to salvage distal flow	
	Endovascular rescue	

Kirtane AJ, Circulation 2016

Then, suddenly came the TWILIGHT ……

TWILIGHT: Study Design Overview[1]



Primary composite endpoint (ITT): Clinically relevant (BARC type 2, 3, or 5) bleeding during months 3-15

Key secondary endpoint (per protocol): Composite of all-cause death, non-fatal MI, stroke during months 3-15[c]

[a]**High-risk patients must meet ≥1 criteria from both clinical and angiographic criteria (Inclusion criteria):**

- **Clinical:** ≥65 years of age, female, troponin positive ACS, established vascular disease (previous MI, documented PAD or CAD/PAD revascularization), DM treated with medications, CKD (eGFR <60 mL/min/1.73 m^2 or CrCl <60 mLmin)
- **Angiographic:** multivessel CAD, target lesion total stent length >30 mm, thrombotic target lesion, bifurcation lesions with Medina X, 1, 1 classification requiring ≥2 stents, left main ≥50% or proximal LAD ≥70% lesion, calcified target lesion requiring atherectomy

[b]**Event-free if none of the following:**

- Major bleeding (≥BARC type 3b); ischemic event after PCI (eg, non-fatal MI, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with DES); no longer taking DAPT with ticagrelor + ASA; non physician-guided cessation of ASA or ticagrelor of ≥5 consecutive days; current indication for oral anticoagulation or high dose ASA; renal failure requiring dialysis; woman of child bearing potential; refusal of randomization by patient or treating physician; withdrawal of consent; lost to follow-up

[c]Other secondary ischemic endpoints included time to first occurrence of: (i) CV death, non-fatal MI, ischemic stroke or clinically-driven revascularization; (ii) CV death, non-fatal MI or ischemic stroke; (iii) definite or probable stent thrombosis; (iv) CV death.

1. Baber U et al. *Am Heart J.* 2016;182:125-134; 2. Mehran R et al. Online ahead of print. *N Engl J Med*. 2019.

TWILIGHT: Inclusion and Exclusion Criteria

Inclusion Criteria

Clinical Criteria (must meet ≥ 1):

- ≥65 years of age
- Female
- Troponin positive ACS
- Established vascular disease (previous MI, documented PAD or CAD/PAD revascularization)
- DM treated with medications
- CKD (eGFR <60mL/min/1.73m^2 or CrCl <60mL/min)

Angiographic Criteria (must meet ≥ 1):

- Multivessel CAD
- Target lesion requiring total stent length >30 mm
- Thrombotic target lesion
- Bifurcation lesions with Medina X,1,1 classification requiring ≥2 stents
- Left main (≥50%) or proximal LAD (≥70%) lesion
- Calcified target lesion(s) requiring atherectomy

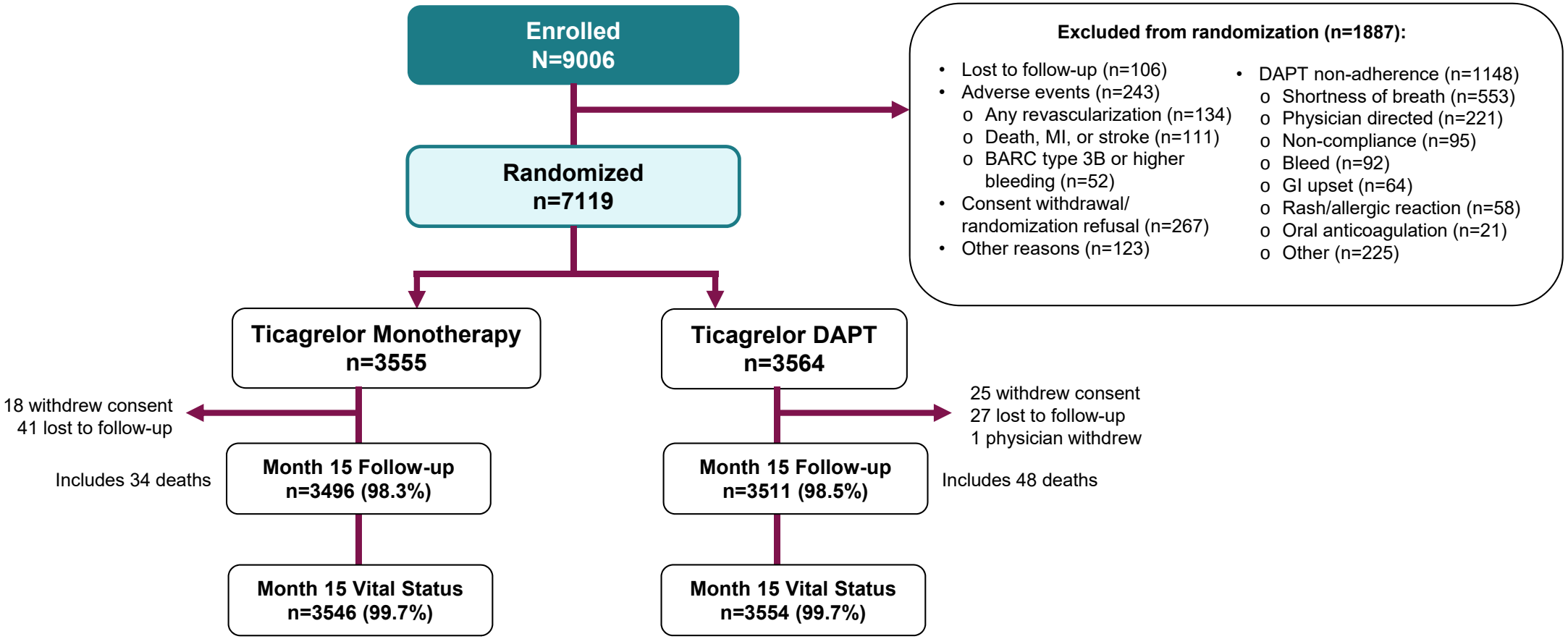
Exclusion Criteria

- <18 years of age
- Contraindication to ASA or ticagrelor
- Planned surgery or coronary revascularization within 90 days
- Need for chronic oral anticoagulation or ongoing ASA ≥325 mg
- Prior stroke
- Dialysis-dependent renal failure or liver cirrhosis
- Active bleeding or extreme-risk for major bleeding
- Salvage PCI or STEMI presentation
- Life expectancy <1 year
- Women of child-bearing potential
- Fibrinolytic therapy within 24 hours of index PCI
- Concomitant therapy with a strong cytochrome P450 3A inhibitor/inducer
- Platelet count <100,000 mm^3

ACS = acute coronary syndrome; ASA = aspirin; CAD = coronary artery disease; CKD = chronic kidney disease; CrCl = creatinine clearance; DM = diabetes mellitus; eGFR = estimated glomerular filtration; LAD = left anterior descending; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Baber U et al. *Am Heart J.* 2016;182:125-134.

TWILIGHT: Patient Distribution



BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; GI = gastrointestinal; MI = myocardial infarction.

Mehran R et al. Article and supplementary appendix online ahead of print. *N Engl J Med*. 2019.

TWILIGHT: Baseline Demographics of the Randomized Population

Characteristic[a]	Ticagrelor Monotherapy (n=3555)	Ticagrelor DAPT (n=3564)
Clinical parameters		
Age, years (mean ± SD)	65.2 ± 10.3	65.1 ± 10.4
Female	846 (23.8)	852 (23.9)
Nonwhite race	1110 (31.2)	1086 (30.5)
BMI, kg/m^2 (mean ± SD)	28.6 ± 5.5	28.5 ± 5.6
Medical history		
Diabetes mellitus	1319 (37.1)	1301 (36.5)
Chronic kidney disease (eGFR <60mL/1.73m^2)	572/3410 (16.8)	573/3425 (16.7)
Anemia	675/3405 (19.8)	654/3423 (19.1)
Current smoker	726/3553 (20.4)	822/3562 (23.1)
Hypercholesterolemia	2157 (60.7)	2146 (60.2)
Hypertension	2580/3555 (72.6)	2574/3563 (72.2)
Peripheral arterial disease	245 (6.9)	244 (6.8)
Previous MI	1020 (28.7)	1020 (28.6)
Previous PCI	1502 (42.3)	1496 (42.0)
Previous CABG	362/3554 (10.2)	348/3564 (9.8)
Multivessel CAD	2272 (63.9)	2194 (61.6)
Previous major bleeding event	31 (0.9)	32 (0.9)
Indication for PCI		
Asymptomatic	234/3554 (6.6)	223/3563 (6.3)
Stable angina	1047/3554 (29.5)	999/3563 (28.0)
Unstable angina	1249/3554 (35.1)	1245/3563 (34.9)
NSTEMI	1024/3554 (28.8)	1096/3563 (30.8)

[a]Data presented as number (%) or number/total number of patients (%) unless otherwise noted.

Mehran R et al. Online ahead of print. *N Engl J Med*. 2019.

TWILIGHT: Baseline Procedural Parameters of the Randomized Population

Procedural Parameters[a]	Ticagrelor Monotherapy (n=3555)	Ticagrelor DAPT (n=3564)
Radial artery access	2600 (73.1)	2586 (72.6)
Multivessel CAD	2272 (63.9)	2194 (61.6)
Number of vessels treated (mean ± SD)	1.3 ± 0.5	1.3 ± 0.5
Number of lesions treated (mean ± SD)	1.5 ± 0.7	1.5 ± 0.7
Total stent length, mm (mean ± SD)[b]	40.1 ± 24.2	39.7 ± 24.3
Minimum stent diameter, mm (mean ± SD)	2.8 ± 0.5	2.9 ± 0.5
2nd generation DES[c]	3477 (97.8)	3481 (97.7)
Total contrast, mL (mean ± SD)	171.8 ± 76.2	174.4 ± 80.1
Target vessel		
LAD	1993 (56.1)	2010 (56.4)
Right coronary artery	1243 (35.0)	1257 (35.3)
Left circumflex	1151 (32.4)	1146 (32.2)
Left main	166 (4.7)	187 (5.2)
Target lesion morphology[d]		
Thrombus	369 (10.4)	380 (10.7)
Moderate or severe calcification	498 (14.0)	489 (13.7)
Bifurcation	434 (12.2)	432 (12.1)
Chronic total occlusion	222 (6.2)	224 (6.3)
Venous bypass graft	62 (1.7)	72 (2.0)

[a]Data presented as number (%) unless otherwise noted; [b]Calculated by operator; [c]Includes the following stent platforms: durable polymer cobalt chromium everolimus eluting stent (EES), durable polymer platinum chromium EES, durable polymer zotarolimus eluting stent, durable polymer cobalt chromium sirolimus eluting stent, biodegradable polymer DES, polymer free DES, bioresorbable vascular scaffold, sirolimus eluting self-apposing stent, tacrolimus eluting Carbostent; [d]Assessed by operators.

Mehran R et al. Supplementary appendix. *N Engl J Med*. 2019.

TWILIGHT: Baseline Demographics of the Enrolled Cohort

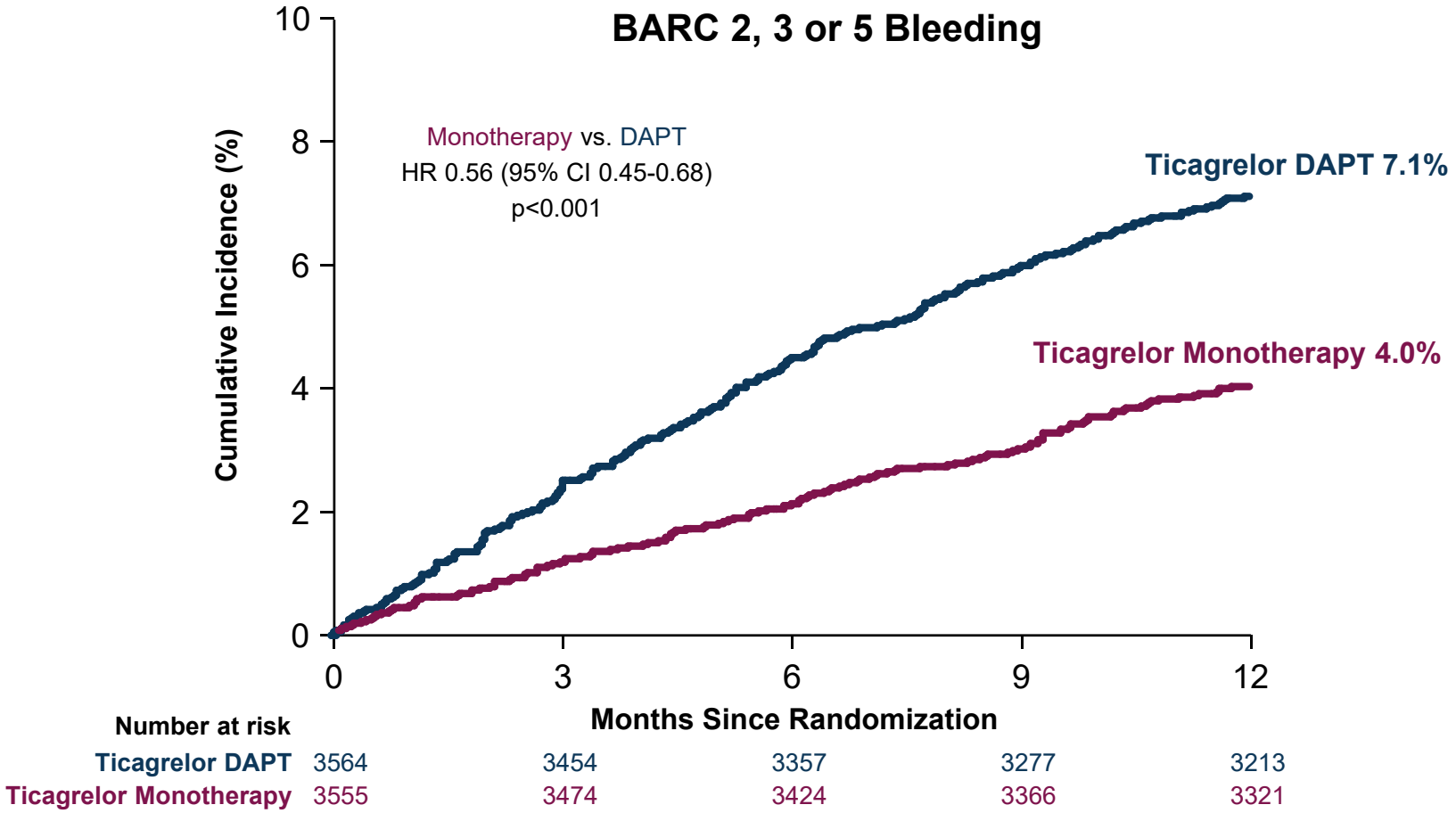
Characteristic[a]	Overall N=9006	Not randomized n=1887	Randomized n=7119
Clinical parameters			
Age, years (mean ± SD)	65.7 ± 10.4	67.7 ± 10.4	65.1 ± 10.3
Female	2235 (24.8)	537 (28.5)	1698 (23.9)
Nonwhite race	2637 (29.3)	441 (23.4)	2196 (30.8)
BMI, kg/m^2 (mean ± SD)	28.7 ± 5.7	29.3 ± 6.1	28.6 ± 5.6
Medical history			
Atrial fibrillation	144 (1.6)	45 (2.4)	99 (1.4)
Diabetes mellitus	3395 (37.7)	775 (41.1)	2620 (36.8)
Current smoker	1899 (21.1)	351 (18.7)	1548 (21.8)
Hypercholesterolemia	5630 (62.5)	1327 (70.3)	4303 (60.4)
Hypertension	6607 (73.4)	1453 (77.0)	5154 (72.4)
Congestive heart failure	530 (5.9)	164 (8.7)	366 (5.1)
Peripheral artery disease	708 (7.9)	219 (11.6)	489 (6.9)
Previous MI	2593 (28.8)	553 (29.3)	2040 (28.7)
Previous PCI	3927 (43.6)	929 (49.2)	2998 (42.1)
Previous CABG	1019 (11.3)	309 (16.4)	710 (10.0)
Previous TIA	176 (2.0)	54 (2.9)	122 (1.7)
Multivessel CAD	5685 (63.1)	1219 (64.6)	4466 (62.7)
Previous major bleed	89 (1.0)	26 (1.4)	63 (0.9)
Renal failure on dialysis	29 (0.3)	11 (0.6)	18 (0.3)
Liver disease	36 (0.4)	9 (0.5)	27 (0.4)

[a]Data presented as number (%) unless otherwise noted.

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; TIA = transient ischemic attack.

Mehran R et al. Supplementary appendix. *N Engl J Med*. 2019.

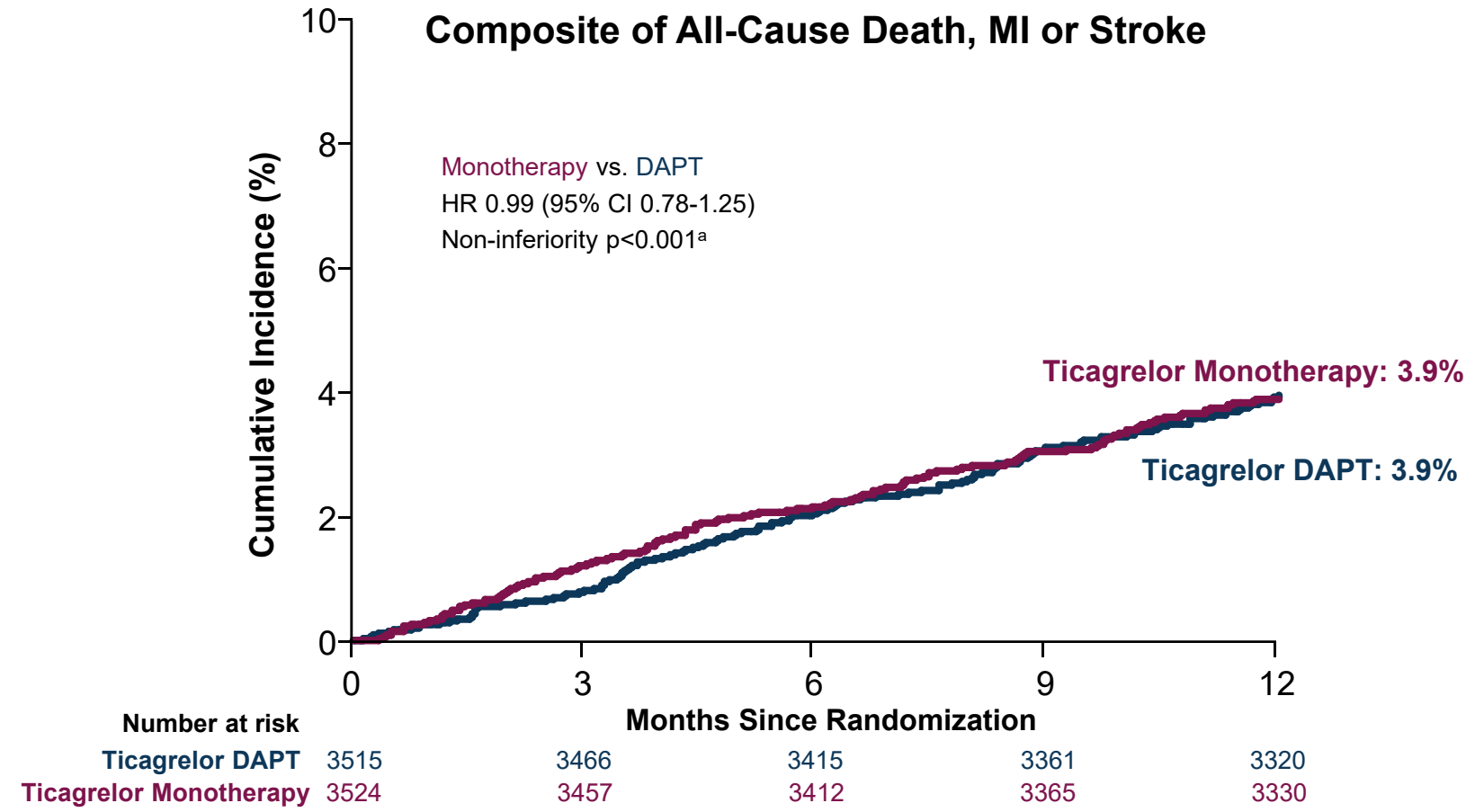
TWILIGHT: Primary Endpoint[1]



Note: The primary endpoint analysis was performed in the ITT cohort, including those who were successfully randomized at the 3-month visit.[2]

1. Mehran R et al. Online ahead of print. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J.* 2016;182:125-134.

TWILIGHT: Key Secondary Endpoint[1]

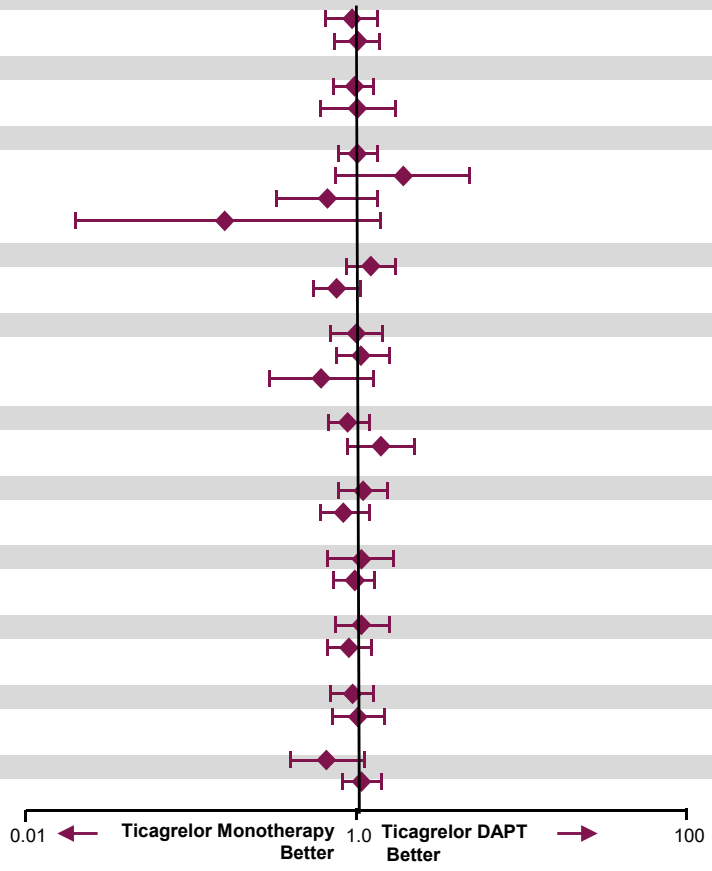


Note: The key secondary endpoint was performed in the per protocol cohort, including those who were randomized and completed all study-related contacts without any major protocol deviations.[2]
[a]Non-inferiority was tested at a one-sided alpha level of 0.025 using 1.6% as the absolute upper limit of the 95% CI.[2]

1. Mehran R et al. Online ahead of print. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J.* 2016;182:125-134.

TWILIGHT: Key Secondary Endpoint (Composite of All-cause Death, MI or Stroke) in Pre-specified Patient Subgroups[1]

		n (%)		
Subgroups	**# of Patients**	**Ticagrelor Monotherapy**	**Ticagrelor DAPT**	**HR (95% CI)**
Age (years)				
<65	3362	56 (3.4)	60 (3.6)	0.94 (0.65-1.35)
≥65	3677	79 (4.3)	77 (4.2)	1.02 (0.75-1.40)
Sex				
Male	5363	106 (4.0)	108 (4.1)	0.98 (0.75-1.29)
Female	1676	29 (3.5)	29 (3.5)	0.99 (0.59-1.66)
Race/Ethnicity				
White	4874	108 (4.5)	106 (4.4)	1.03 (0.79-1.35)
Black	267	13 (10.2)	7 (5.4)	1.91 (0.76-4.79)
Asian	1757	13 (1.5)	19 (2.2)	0.67 (0.33-1.35)
Other	141	1 (1.3)	5 (7.8)	0.16 (0.02-1.41)
Diabetes Mellitus				
No	4446	76 (3.5)	62 (2.8)	1.24 (0.89-1.73)
Yes	2593	59 (4.6)	75 (5.9)	0.77 (0.55-1.09)
Region of Enrollment				
North America	2939	62 (4.3)	62 (4.3)	1.00 (0.70-1.42)
Europe	2487	61 (5.0)	56 (4.5)	1.10 (0.77-1.59)
Asia	1613	12 (1.5)	19 (2.4)	0.62 (0.30-1.29)
CKD (eGFR <60 ml/min)				
No	5629	90 (3.2)	100 (3.6)	0.90 (0.68-1.20)
Yes	1133	43 (7.7)	31 (5.5)	1.40 (0.88-2.22)
BMI (kg/m^2)				
Below Median	3520	72 (4.1)	65 (3.7)	1.11 (0.80-1.56)
Above Median	3490	62 (3.6)	72 (4.2)	0.85 (0.61-1.20)
Indication for PCI				
Stable	2472	39 (3.1)	35 (2.9)	1.06 (0.67-1.67)
ACS	4565	96 (4.3)	102 (4.5)	0.97 (0.73-1.28)
Total Stent Length (mm)				
<30	3003	59 (4.0)	56 (3.7)	1.10 (0.76-1.58)
≥30	4036	76 (3.8)	81 (4.1)	0.91 (0.67-1.24)
Prior MI				
No	5020	77 (3.1)	81 (3.3)	0.95 (0.70-1.30)
Yes	2019	58 (5.8)	56 (5.6)	1.03 (0.72-1.49)
Multivessel Disease				
No	2392	23 (2.0)	37 (3.0)	0.67 (0.40-1.12)
Yes	4647	112 (4.8)	100 (4.4)	1.08 (0.83-1.42)

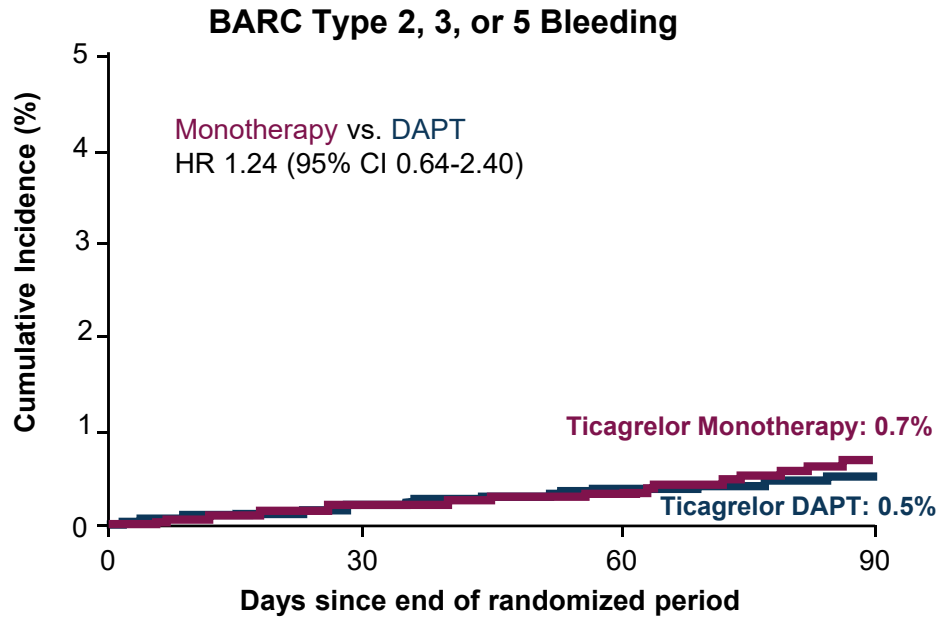


Note: Ischemic endpoints were performed in the per protocol cohort, including those who were randomized and completed all study contact visits.[2]

1. Mehran R et al. Supplementary appendix. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J.* 2016;182:125-134.

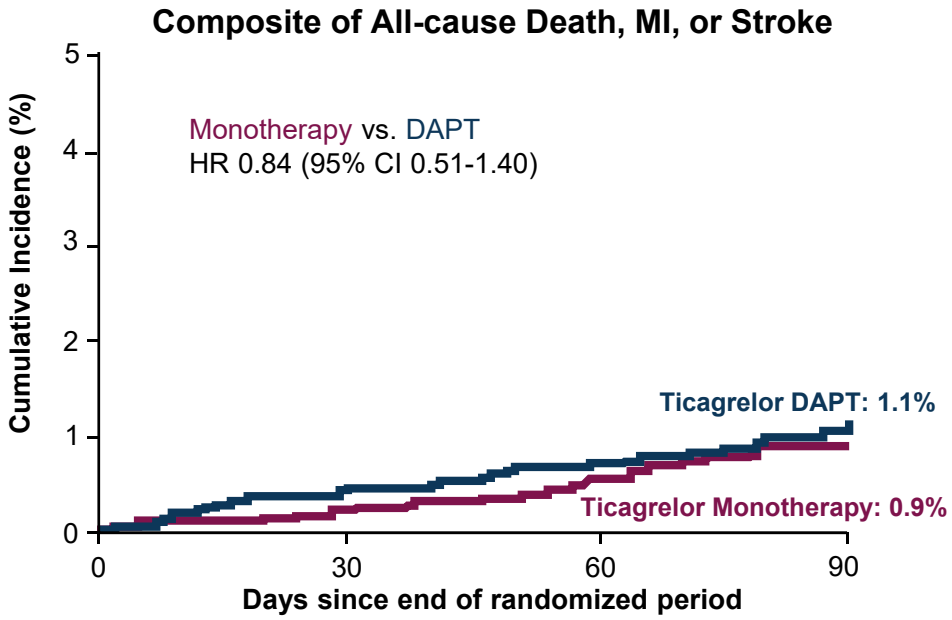
TWILIGHT: Landmark Analyses Between 15 and 18 Months After PCI (Observational Period)

Low bleeding event rate overall; no difference in BARC 2, 3 or 5 bleeding during the observational period



Number at risk				
DAPT	3454	3424	3359	994
Monotherapy	3456	3437	3386	1060

No difference in composite ischemic events during the observational period



Number at risk				
DAPT	3454	3428	3364	993
Monotherapy	3456	3443	3388	1063

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Mehran R et al. Supplementary appendix. *N Engl J Med*. 2019.

TWILIGHT: Conclusions

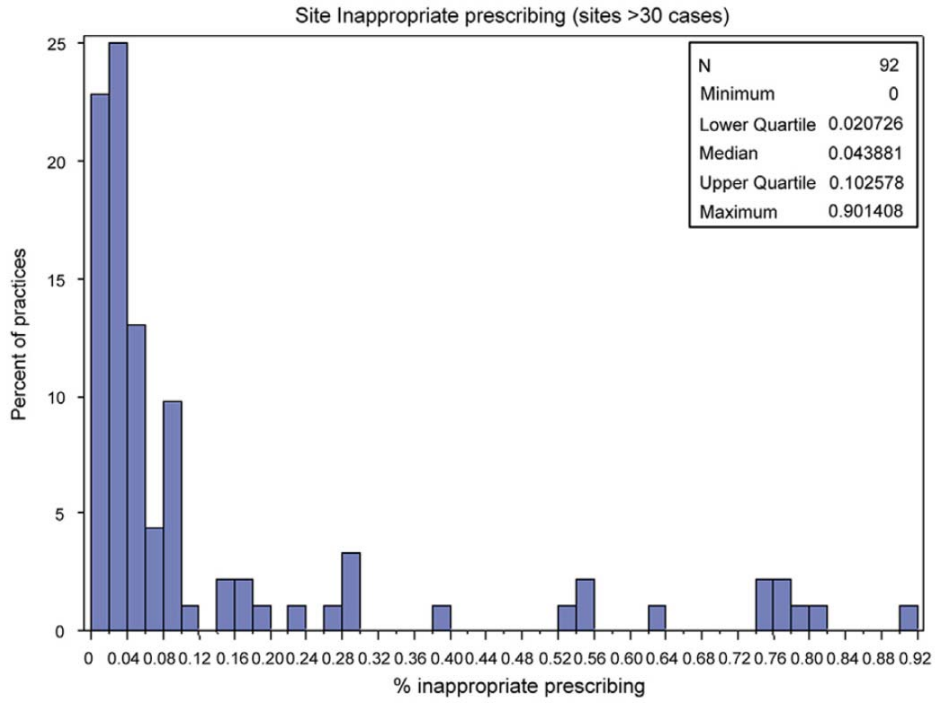
- **TWILIGHT gave the insight of possibly doing of ticagrelor monotherapy in patients with complex coronary disease(major component of CHIP) with or without ACS.**
- **To avoid bleeding issues, the study subjects had a 3-months period whether they tolerated ticagrelor DAPT, to be enrolled into the study.**
- **As long as successfully enrolled, ticagrelor monotherapy is better reducing bleeding events as compared with ticagrelor DAPT.**

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Mehran R et al. Online ahead of print. *N Engl J Med*. 2019.

Off-Label Use of Potent P2Y12 Inhibitor in Real World

- *NCDR PINNACLE Registry* (US national, prospective, quality improvement registry). Analysis of patients from 123 practices between July 1, 2009 and June 13, 2013)
- Definition: prasugrel use in patients with documented history of prior TIA/stroke(inappropriate). Prasugrel use in patients >75 years of age without DM or a previous MI(non-recommended)
- 27,533 patients received prasugrel; 3,824(13.9%) – inappropriate indication, 1,210(4.4%) – non-recommended indication
- Possible explanation of off-label use: inappropriate(higher rate of private insurance), non-recommended(higher prevalence of comorbidities, such as DM, hypertension, dyslipidemia, AF, HF, PAD and CABG surgery)



Hira RS, JACC 2014

Off-Label Use of Potent P2Y12 Inhibitor in Real World

- *OptumInsight Clinformatics Data Mart* (US commercial health insurance database with >15 million enrollees annually). Using administrative claims from Jan 1, 2009

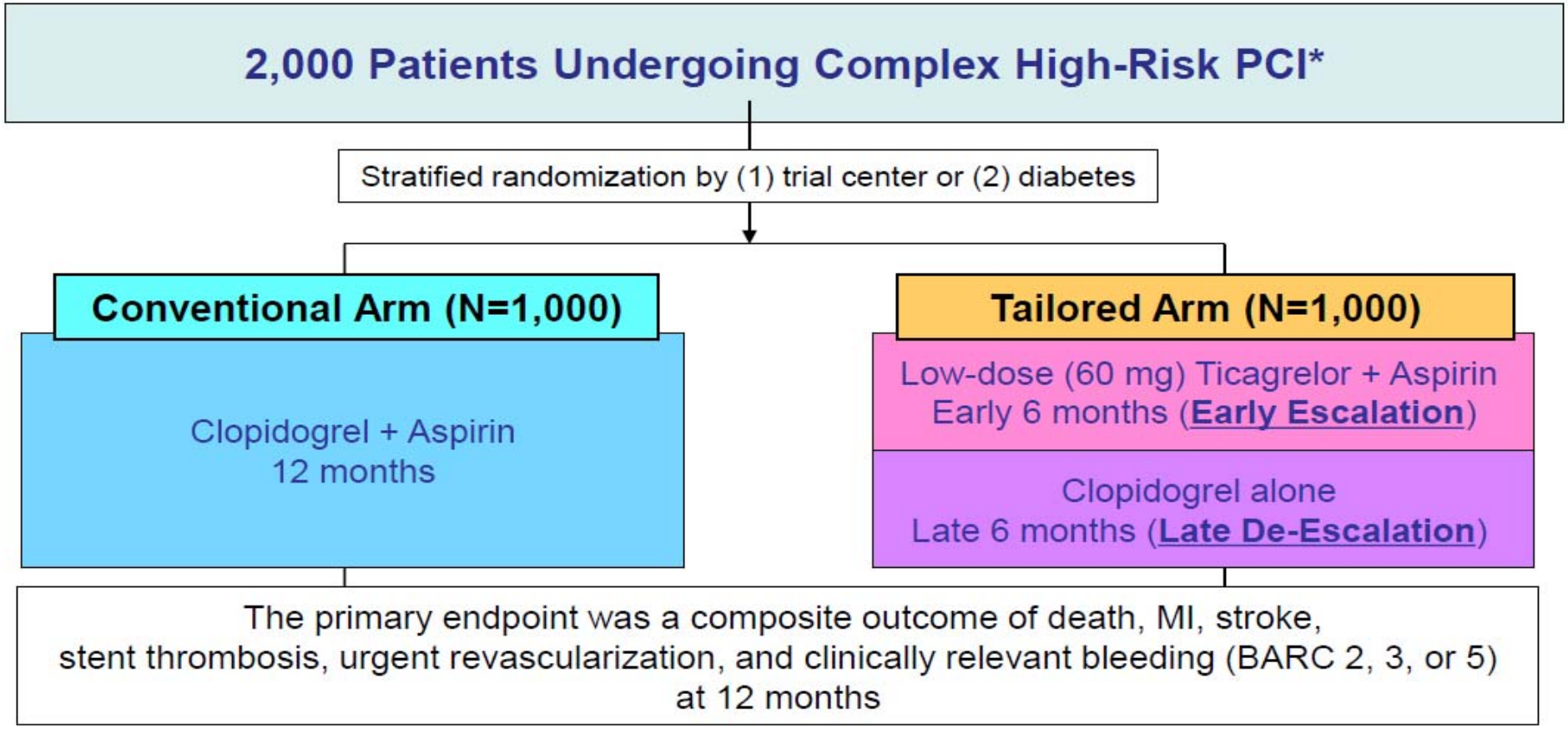
- In the real world, patients without ACS underwent PCI in the US were prescribed with prasugrel or ticagrelor for various reasons.
- The status of poor or intermediate metabolizer of clopidogrel by pharmacogenomic test may be one of the reasons of using prasugrel or ticagrelor in non-ACS setting.
- On-going trials such as ALPHEUS(*NCT02617290*) will determine the role of potent P2Y12 inhibitors for elective PCI.
- May need to take extra efforts to convince regulatory body(i.e. KFDA) for this off-label use.

a prescription within 30 days of discharge for clopidogrel, prasugrel, and ticagrelor, respectively. **A**, Includes patients with a nonacute coronary syndrome (ACS) indication for PCI (n=6959), and (**B**) includes patients with ACS as indication for PCI (n=35 724).

Dayoub EJ et al, Circ Cardiovasc Interv 2019

TAILored versus C***O***nventional Antith***R***ombotic Strat***E***gy
Inten***D***ed for ***C***omplex ***HI***gh-Risk ***P***CI

TAILORED-CHIP Trial



***Complex High-Risk PCI**

: Left main PCI, chronic total occlusion, bifurcation with 2 stents implanted, severe calcification, diffuse long lesion (lesion length ≥ 30mm), multivessel PCI (≥ 2 vessels stented), ≥**3** stents implanted, ≥**3** lesions treated, total stent length >60mm, diabetes, CKD (Cr-clearance <60ml/min) or severe LV dysfunction (EF <40%).

Courtesy of Park DW

Enigma of Antiplatelet Strategy (*in my opinion*)

ACS	**Potent P2Y12 inhibitor(prasugrel/ticagrelor) >> clopidogrel 12 months DAPT >> less than 12 months DAPT(?)**
Non-ACS	**Clopidogrel >> potent P2Y12 inhibitor (in CHIP or comorbid condition or CYP2C19 LOF alleles ?) 6 months DAPT >> 3 months, 12 months or more than 12 months**
HBR	**Clopidogrel > potent P2Y12 inhibitors(prasugrel/ticagrelor) Non-ACS: less DAPT duration (1-3 months) ACS: ???**
Complex lesions (CHIP)	**Clopidogrel > potent P2Y12 inhibitors(prasugrel/ticagrelor)(in more complex lesions ??) 12 months DAPT > more than 12 months DAPT(?)**

Summary

- CHIP is rather a cluster of patients with complex coronary anatomy including high-risk CAD and/or structural heart disease.
- Antiplatelet therapy in CHIP setting remains itself as having an adjunctive role, which is no different from conventional stable IHD in the guidelines.
- Therefore, clopidogrel as a P2Y12 inhibitor with aspirin remains as the standard of care even in CHIP, as well as the duration of DAPT which is same as non-CHIP.
- Recent RCT such as TWILIGHT study highlighted the safety and efficacy of potent P2Y12 inhibitor in high-risk CAD patients including those with non-ACS setting. In the real world, off-label use of potent P2Y12 inhibitor in elective PCI is not uncommon.
- Dedicated study to investigate the benefit of potent P2Y12 inhibitor in high-risk CAD or CHIP setting such as TAILORED-CHIP trial may give insights in the future.


Thanks for Your Attention
Nov 18, 2019 (Ghandruk, Nepal)