# Escalation and De-Escalation Strategy for CHIP-PCI Patients:

## Temporal Tuning in the TAILORED-CHIP Trial

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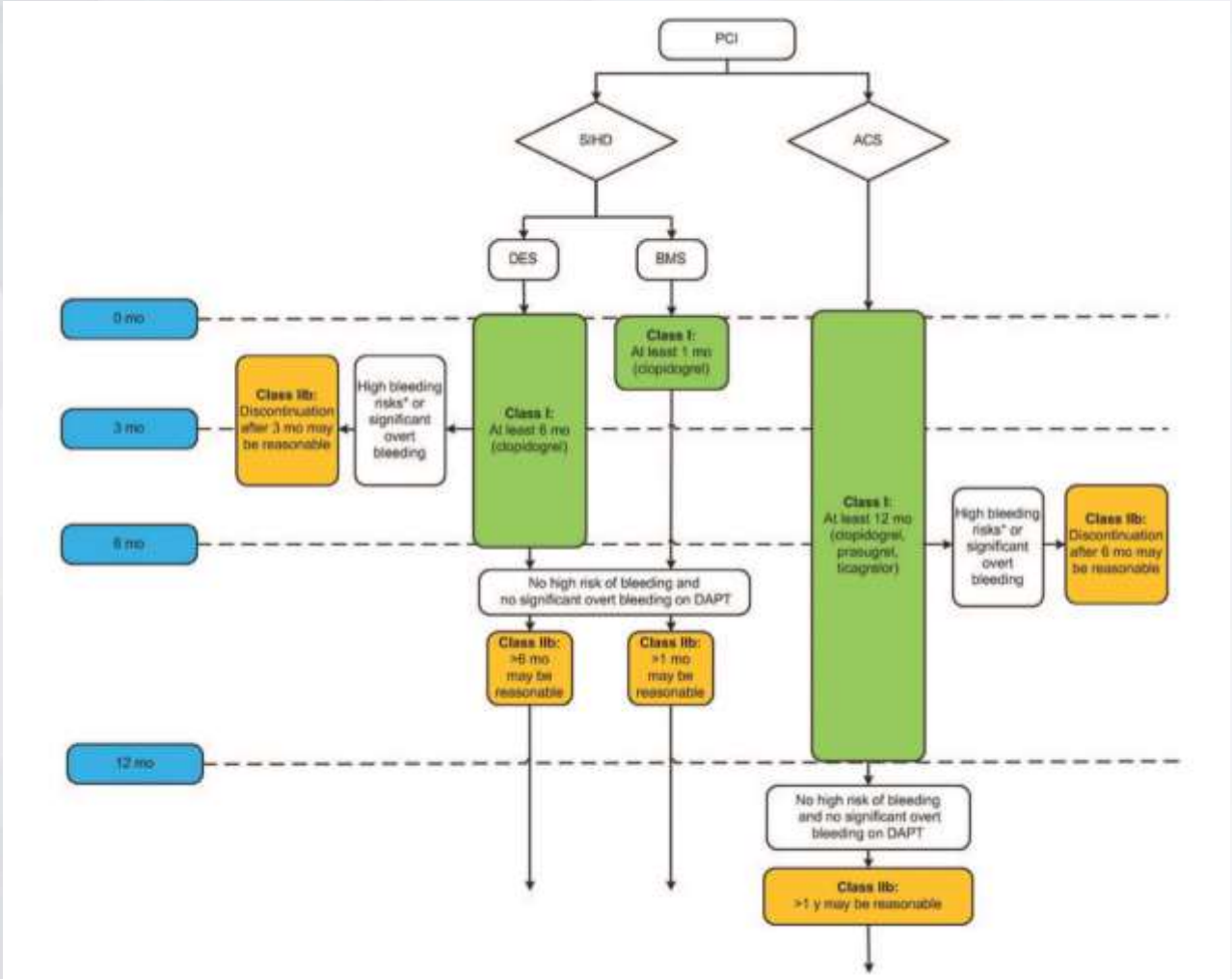
# Disclosure

- Institutional grant/research funding to CardioVascular Research Foundation (CVRF, Korea) and/or Asan Medical Center from Daiichi-Sankyo, HK InnoN, Abbott, Boston Scientific, Medtronics, Edwards, ChongKunDang Pharm and Daewoong Pharm.

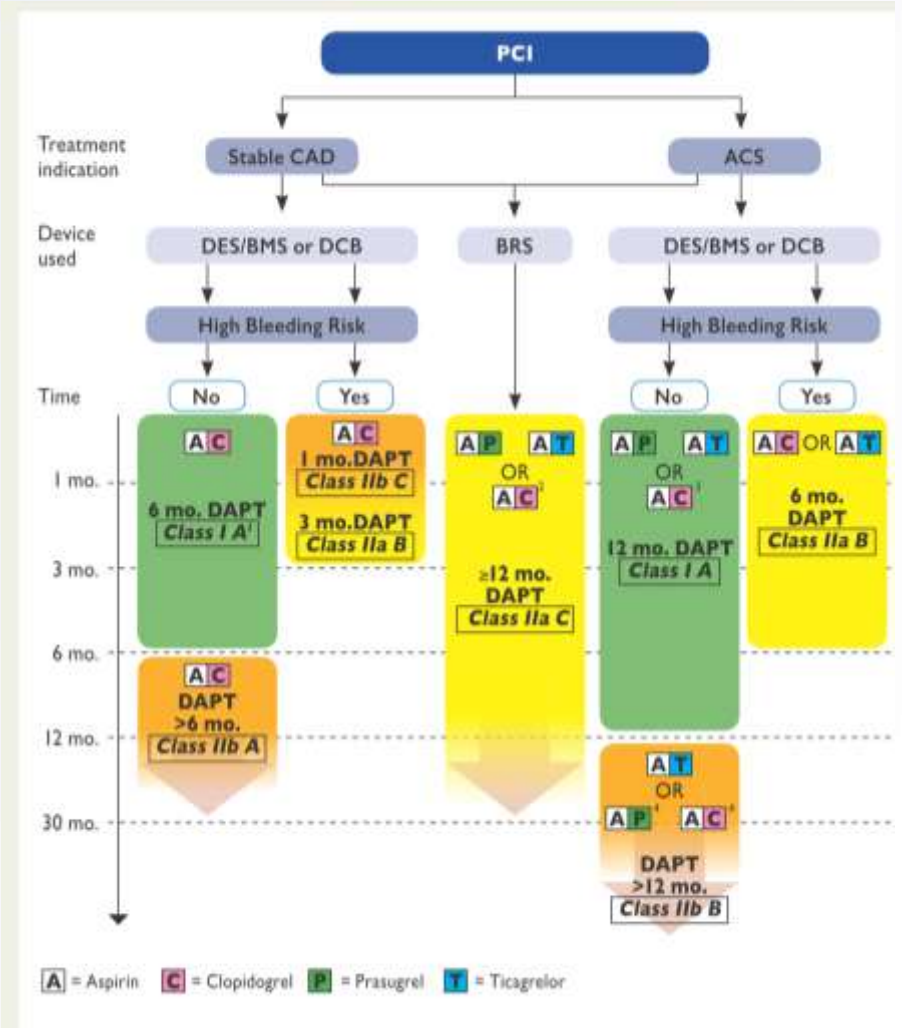
# DAPT Practice Guidelines Are Relatively Simple; Based on (1) ACS vs. Stable, (2) HBR – Yes or No

## 2016 ACCF/AHA/SCAI




J Am Coll Cardiol 2016;68:1082–115

## 2017 ESC/EACTS



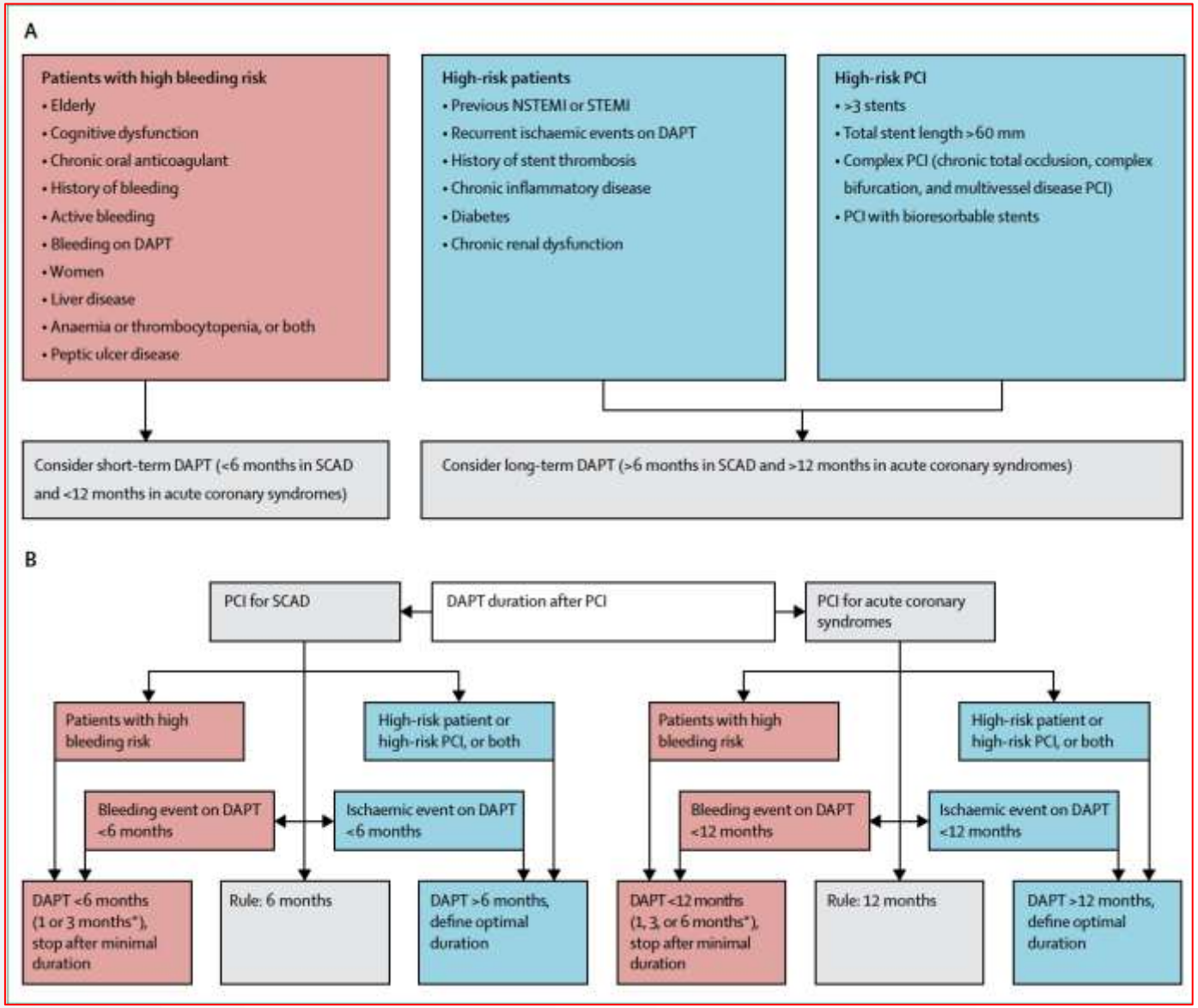

EHJ 2018;39:213–254

# Real-World Practice Is Not Simple

**TABLE 4** Clinical and Procedural Factors Associated With Increased Ischemic Risk (Including Stent Thrombosis) or Increased Bleeding Risk (62-70)

| Increased Ischemic Risk/Risk of Stent Thrombosis (may favor longer-duration DAPT) | Increased Bleeding Risk (may favor shorter-duration DAPT) |
|---|---|
| **Increased ischemic risk** | History of prior bleeding |
| Advanced age | Oral anticoagulant therapy |
| ACS presentation | Female sex |
| Multiple prior MIs | Advanced age |
| Extensive CAD | Low body weight |
| Diabetes mellitus | CKD |
| CKD | Diabetes mellitus |
| **Increased risk of stent thrombosis** | Anemia |
| ACS presentation | Chronic steroid or NSAID therapy |
| Diabetes mellitus | |
| Left ventricular ejection fraction <40% | |
| First-generation drug-eluting stent | |
| Stent undersizing | |
| Stent underdeployment | |
| Small stent diameter | |
| Greater stent length | |
| Bifurcation stents | |
| In-stent restenosis | |

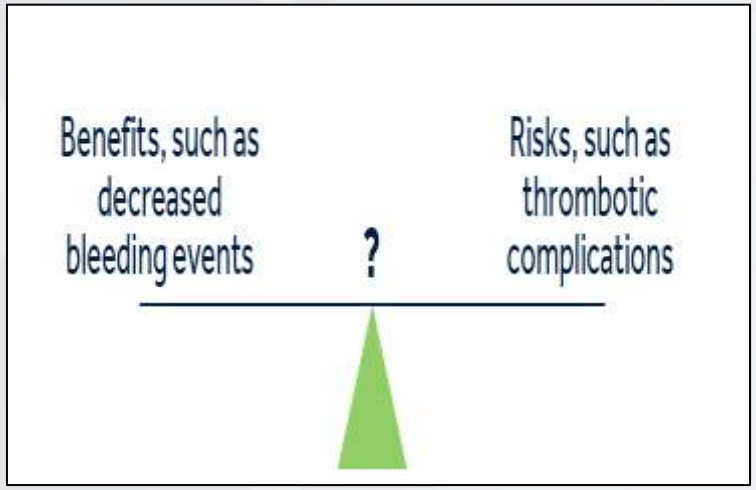
J Am Coll Cardiol 2016;68:1082–115




Lancet 2017; 390: 810–20

# Ischemic & Bleeding Balancing Is Much Complex in "Real-World" Setting

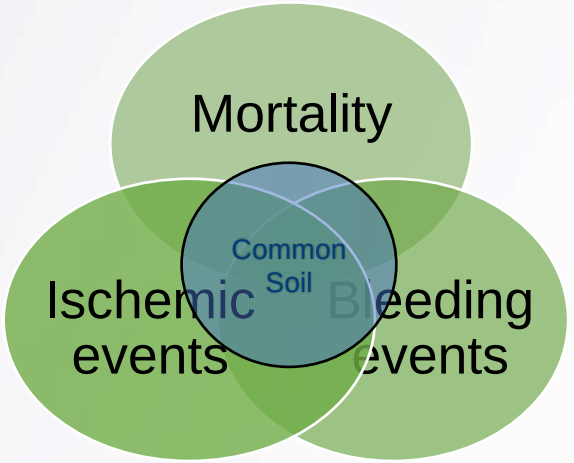
## Theory




"Good Leverage"

## Reality

**Clustering effect**




"Bad Leverage"

# Theory – One Recipe in RCT / CPG Settings


# Reality – Diverse / Different Recipes in the Real-World Setting (Individualizing Treatment Decisions)

# Last 10 Years, Multiple RCTs for Tailored Antithrombotic Strategies in High-Risk (Ischemic or Bleeding) PCI Patients

- Aspirin omission, Ticagrelor mono (De-Escalation): TWILIGHT, GLOBAL-LEADERS, TICO, etc.
- Short DAPT, Clopidogrel mono (De-Escalation): SMART-CHOICE, STOPDAPT-2, etc.
- Dose reduction (De-Escalation): HOST-REDUCE-POLYTECH-ACS, etc.
- PCI & AF (Novel drugs): PIONEER-AF, RE-DUAL PCI, AUGUSTUS, ENTRUST-AF PCI, etc.
- PCI & Stable CAD and/or DM (Escalation): COMPASS, THEMIS, ALPHEUS, etc.

# Recent Trials with Ticagrelor for High-Risk PCI or Patients

- **TWILIGHT:** High-risk PCI for ischemic or bleeding complications
- **THEMIS-PCI**: Type 2 DM and CAD/PCI
- **ALPHEUS:** High-risk elective PCI
- **TAILORED-CHIP:** CHIP-PCI Patients

# TWILIGHT Trial for High-Risk PCI


## Ticagrelor With AspIrin or ALone In HiGH-Risk Patients After Coronary InTervention

*Roxana Mehran, MD*
*@Drroxmehran*
**on behalf of the TWILIGHT Investigators**
Icahn School of Medicine at Mount Sinai, New York, NY

Mount Sinai

*ClinicalTrials.gov Number: NCT02270242*

twilight



Mehran et al. N Engl J Med. 2019;381:2032-2042

# TWILIGHT Inclusion Criteria

Patients undergoing successful PCI with at least 1 locally-approved DES whom the treating clinician intended to discharge on ticagrelor plus aspirin were enrolled in the study

## Clinical criteria

- Age ≥65 years
- Female gender
- Troponin positive ACS
- Established vascular disease (previous MI, documented PAD or CAD/PAD revasc)
- DM treated with medications or insulin
- CKD (eGFR <60ml/min/1.73m$^2$ or CrCl <60ml/min)

## Angiographic criteria

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

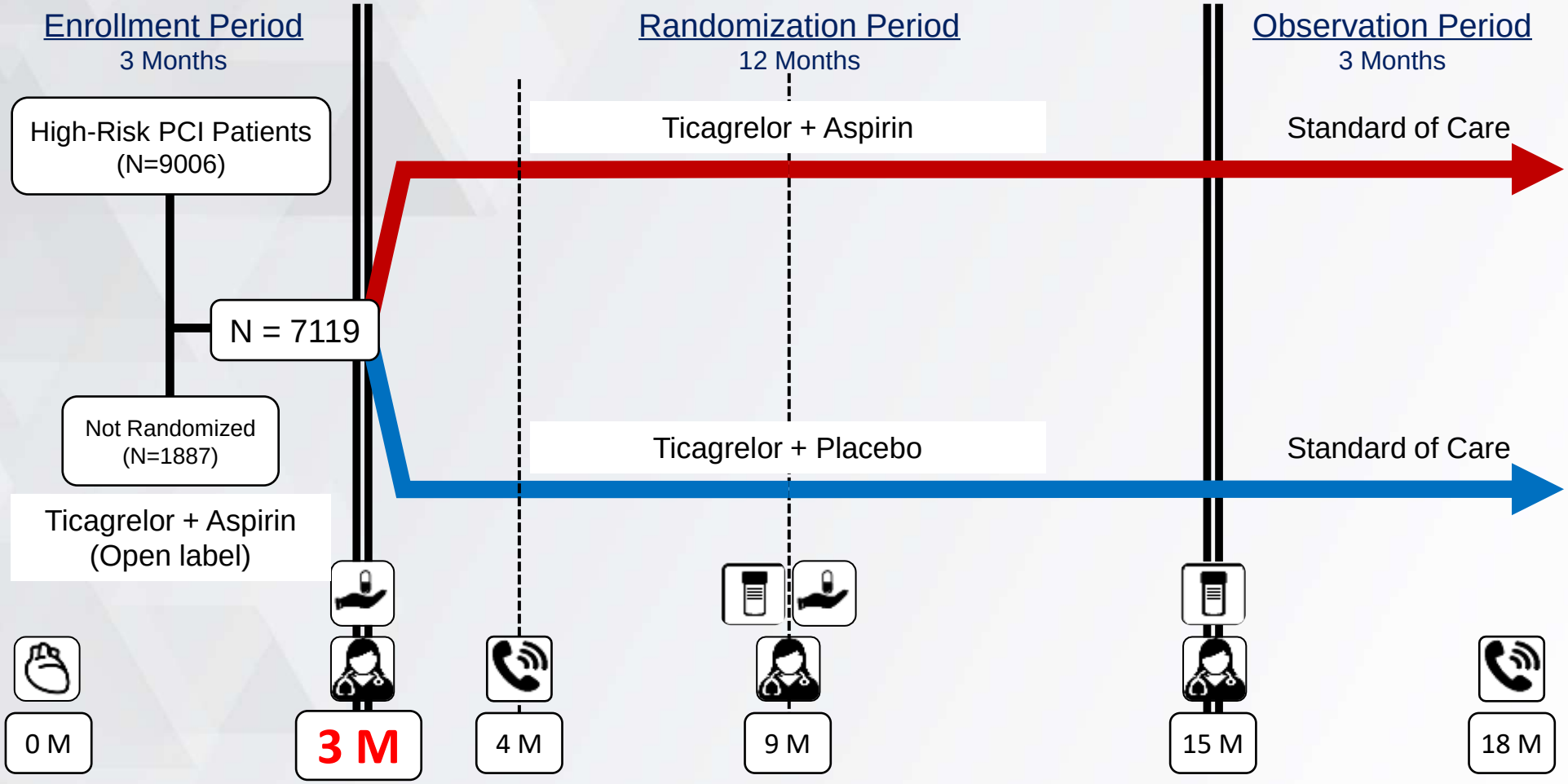
Trial inclusion required the presence of at least 1 additional clinical *AND* angiographic feature associated with a high risk of ischemic or bleeding events.



Mehran et al. N Engl J Med. 2019;381:2032-2042

# TWILIGHT

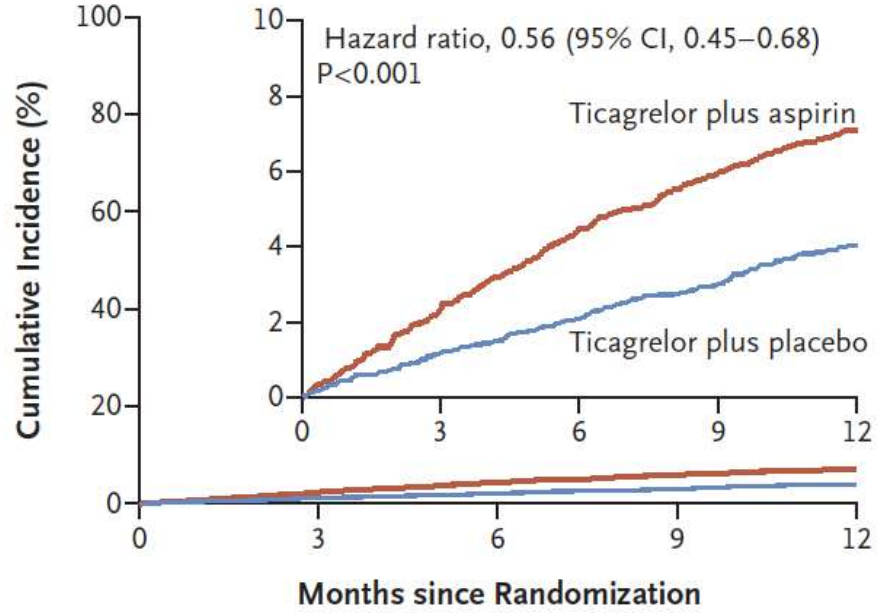
## Study Design




Mehran et al. N Engl J Med. 2019;381:2032-2042

# Primary Endpoint: BARC 2, 3 or 5 Bleeding

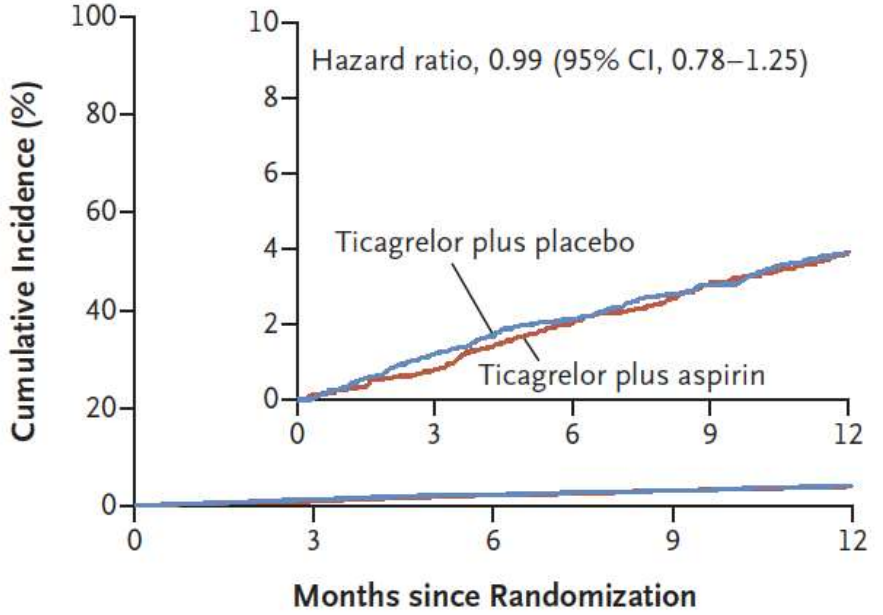
## ITT Cohort




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Ticagrelor plus aspirin | 3564 | 3454 | 3357 | 3277 | 3213 |
| Ticagrelor plus placebo | 3555 | 3474 | 3424 | 3366 | 3321 |

# Secondary Endpoint: Death, MI or Stroke

## PP Cohort




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Ticagrelor plus aspirin | 3515 | 3466 | 3415 | 3361 | 3320 |
| Ticagrelor plus placebo | 3524 | 3457 | 3412 | 3365 | 3330 |

# THEMIS-PCI: Ticagrelor Added to Aspirin in Patients with Diabetes and Stable Coronary Artery Disease with a History of Prior Percutaneous Coronary Intervention


## Presented by Ph. Gabriel Steg, MD

Deepak L. Bhatt,* Philippe Gabriel Steg,*

Shamir R. Mehta, Lawrence A. Leiter, Tabassome Simon, Kim Fox, Claes Held, Marielle Andersson, Anders Himmelmann, Wilhelm Ridderstråle, Jersey Chen, Yang Song, Rafael Diaz, Shinya Goto, Stefan K James, Kausik K. Ray, Alexander Parkhomenko, Mikhail N. Kosiborod, Darren K. McGuire, Robert A. Harrington,

on behalf of the THEMIS Steering Committee and Investigators

*co-Chairs and co-Principal Investigators of THEMIS



**European Society of Cardiology 2019**

ClinicalTrials.gov registration: NCT01991795


HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

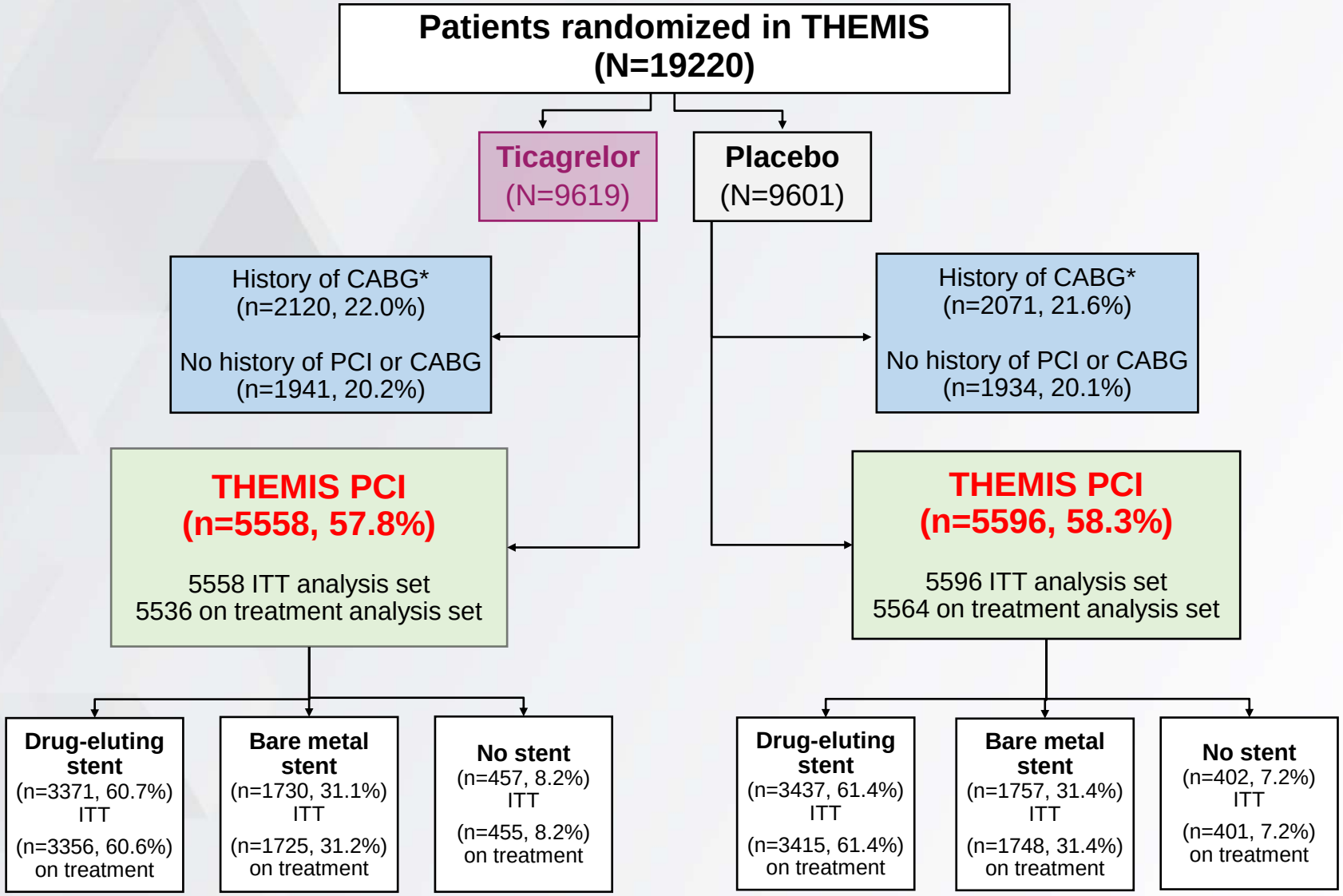
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS


**Bhatt DL, Steg PG, et al. Lancet 2019 2019 Sep 28;394(10204):1169-1180.**


TICAGRELOR IN STABLE CAD AND T2D TREATED WITH ASA

THEMIS

# Study Flow




*excludes patients with a history of PCI; CABG=coronary artery bypass graft; ITT=intention to treat; PCI=percutaneous coronary intervention

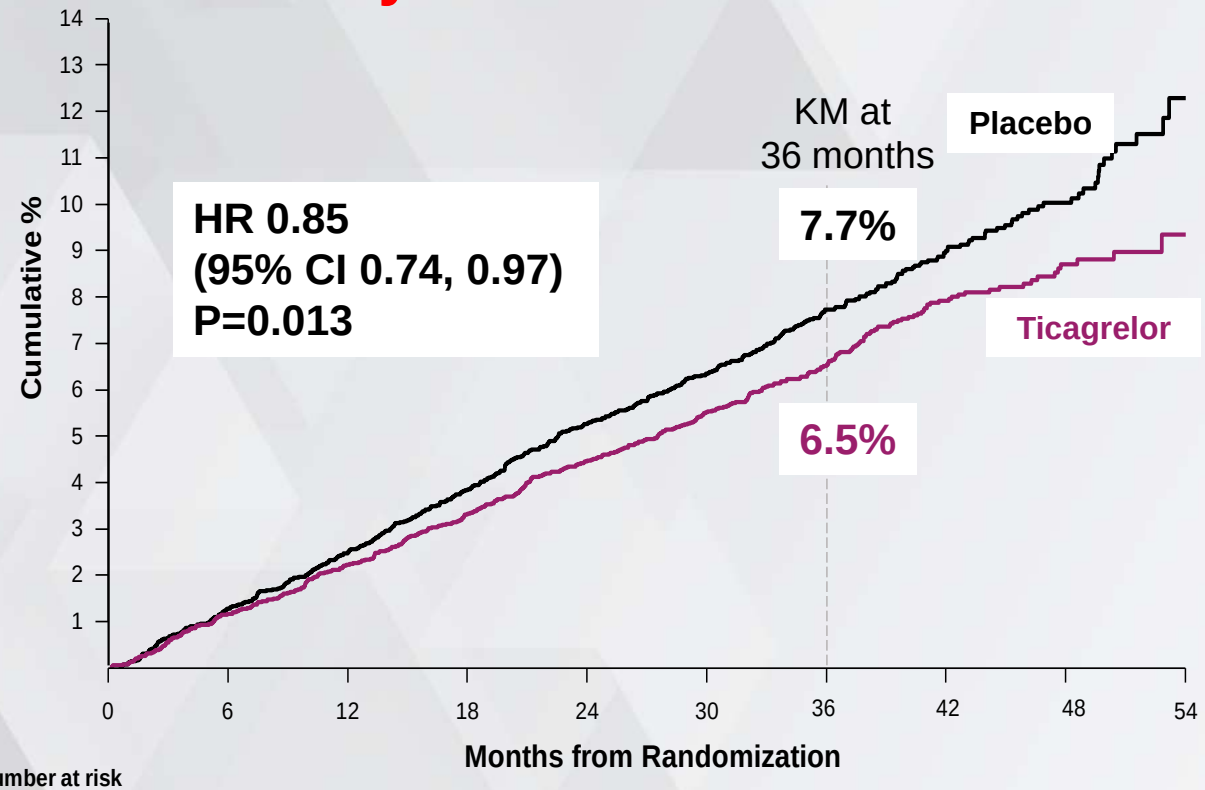
**Bhatt DL, Steg PG, et al. Lancet 2019 2019 Sep 28;394(10204):1169-1180.**

# Primary Efficacy Endpoint

## CV death/MI/stroke (ITT)

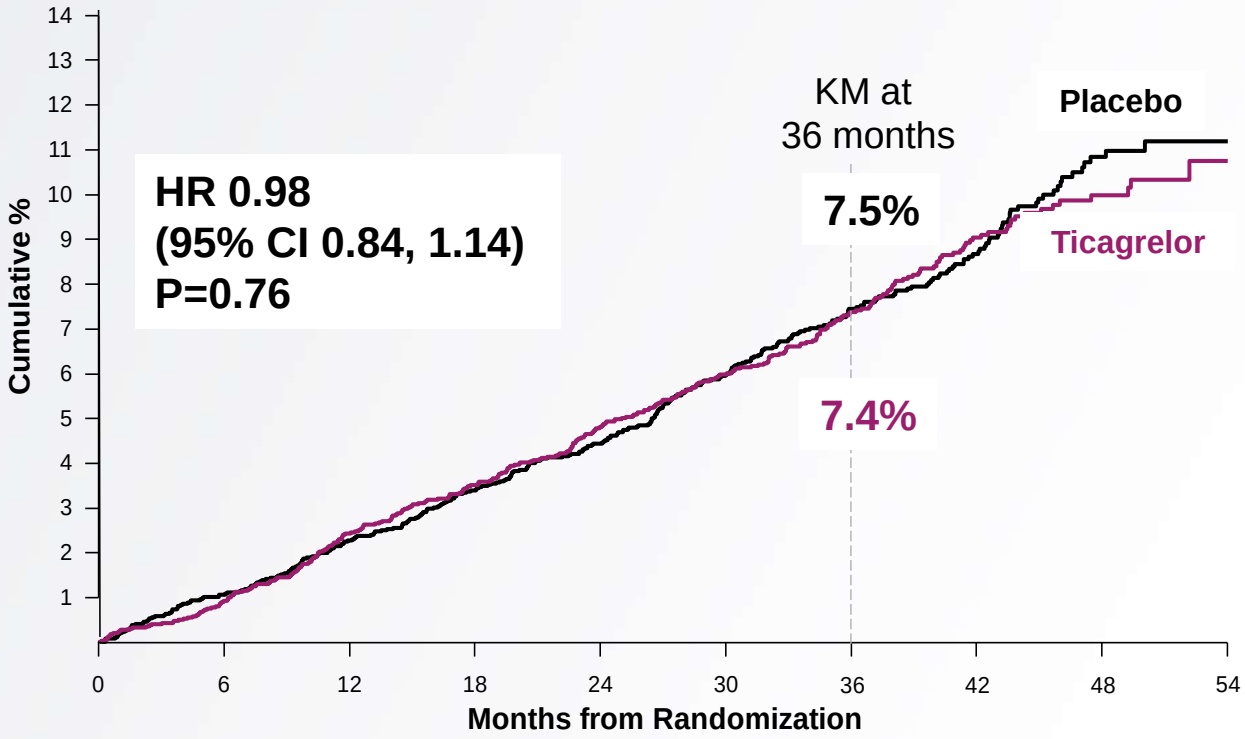
**Interaction p=0.16**

### History of PCI




| Number at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ticagrelor | 5558 | 5436 | 5347 | 5251 | 5165 | 5054 | 3492 | 2128 | 984 | 102 |
| Placebo | 5596 | 5484 | 5387 | 5278 | 5169 | 5062 | 3476 | 2131 | 995 | 103 |

### No History of PCI




| Number at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ticagrelor | 4061 | 3980 | 3890 | 3823 | 3744 | 3638 | 2482 | 1536 | 700 | 68 |
| Placebo | 4005 | 3930 | 3859 | 3798 | 3740 | 3630 | 2458 | 1551 | 690 | 71 |

CI=Confidence Interval; CV=cardiovascular; HR=hazard ratio; KM=Kaplan-Meier; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention



**Bhatt DL, Steg PG, et al. Lancet 2019 2019 Sep 28;394(10204):1169-1180.**

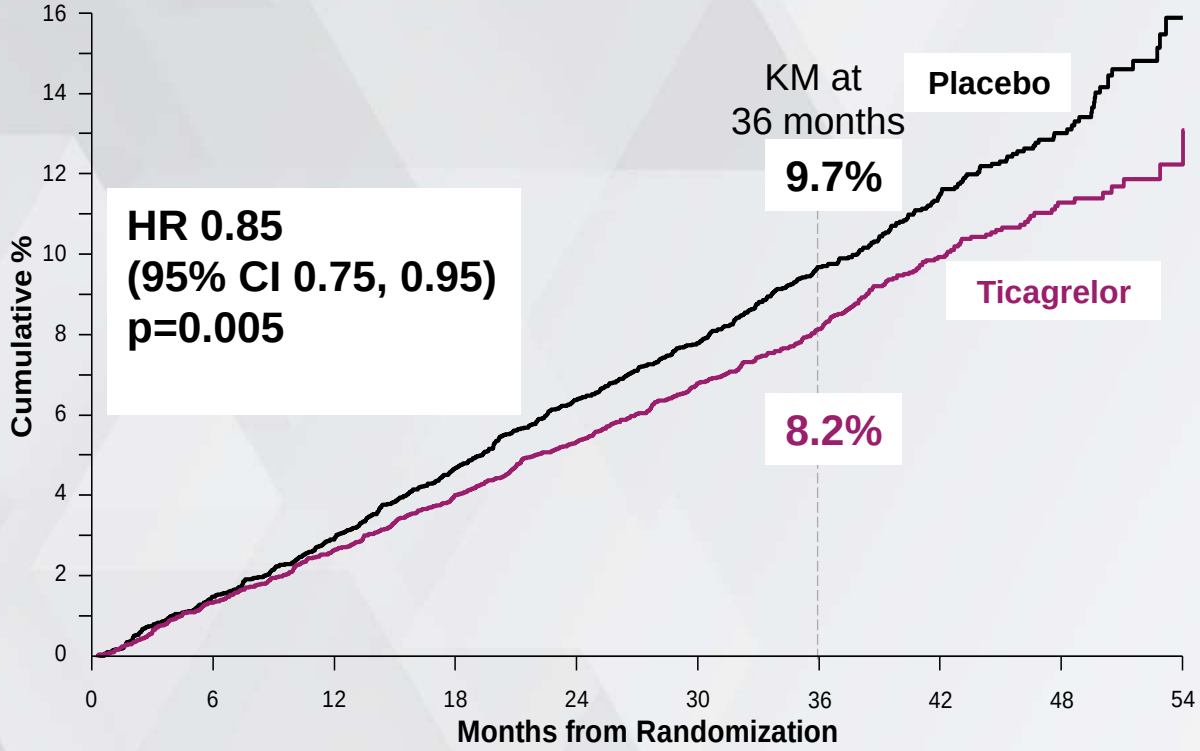
# Net Clinical Benefit

## All cause death, MI, stroke, fatal bleed, or ICH (ITT)*

**History of PCI**

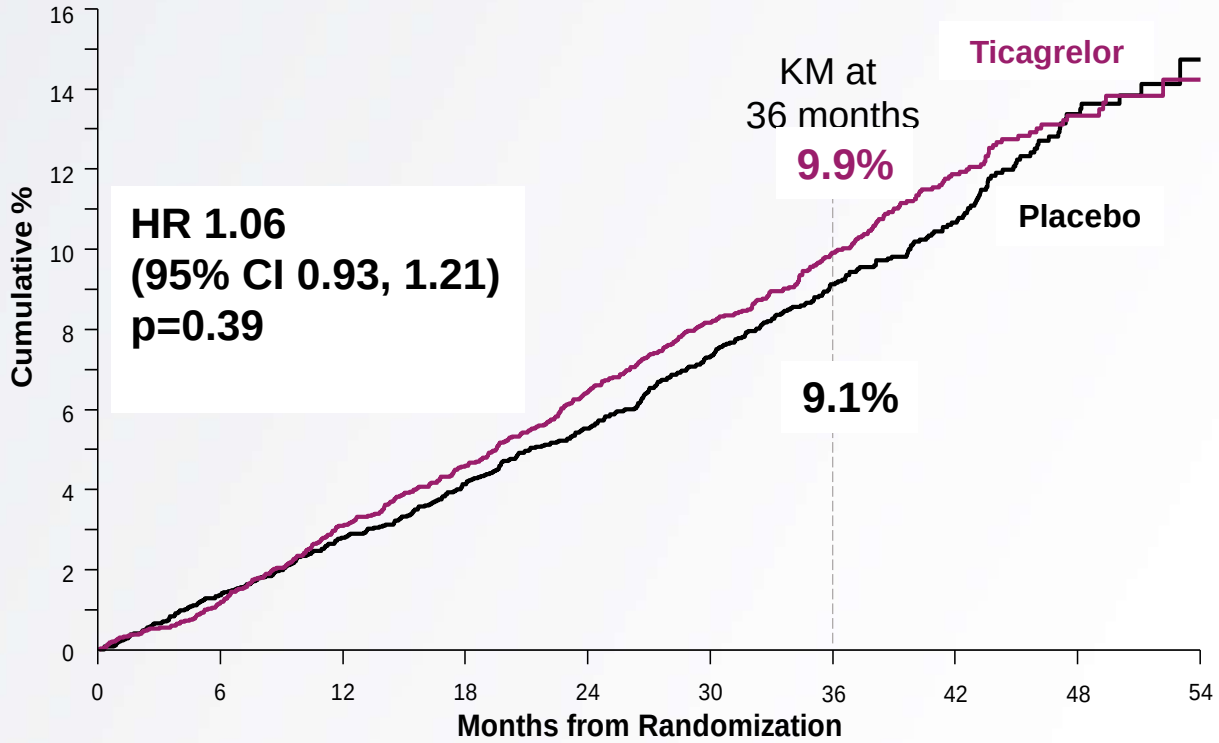
**Interaction p=0.012**

**No history of PCI**




Number at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ticagrelor | 5558 | 5433 | 5339 | 5240 | 5153 | 5037 | 3484 | 2124 | 981 | 100 |
| Placebo | 5596 | 5480 | 5390 | 5274 | 5166 | 5060 | 3470 | 2128 | 993 | 102 |




Number at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ticagrelor | 4061 | 3978 | 3881 | 3813 | 3728 | 3620 | 2471 | 1527 | 696 | 68 |
| Placebo | 4005 | 3932 | 3859 | 3799 | 3737 | 3628 | 2455 | 1549 | 690 | 70 |

*Prespecified definition of net clinical benefit.

CI=confidence interval; HR=hazard ratio; ICH=intracranial hemorrhage; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention



**Bhatt DL, Steg PG, et al. Lancet 2019 2019 Sep 28;394(10204):1169-1180.**

# ALPHEUS

## Assessment of Loading with the P2Y12 inhibitor ticagrelor or clopidogrel to Halt ischemic Events in patients Undergoing elective coronary Stenting

**Johanne Silvain MD-PhD,** Guillaume Cayla MD-PhD, Farzin Beygui MD-PhD, Grégoire Rangé MD, Zuzana Motovska MD-PhD, Eric Vicaut MD-PhD and Gilles Montalescot MD-PhD

**on behalf of the ALPHEUS investigators**

ACTION Group

Academic Research Organization

www.action-cœur.org

ClinicalTrials.gov number, NCT02617290.

@docjohanne

# Inclusion Criteria

- Male or non-pregnant female ≥ 18 years of age
- Undergoing **non-emergent PCI**
- Having **at least one high-risk feature**
- **Negative troponin** or moderately positive and decreasing **before PCI**
- Informed consent obtained in writing at enrolment into the study

**Patient related**

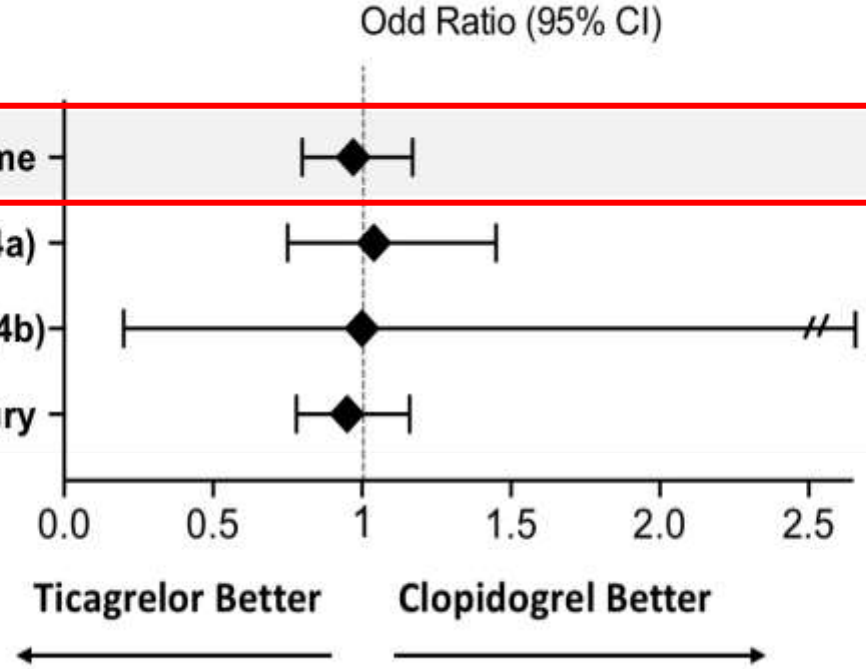
Age > 75
Creat Clearance < 60ml/min
Diabetes Mellitus
BMI >30
History of ACS in the past 12 months
LVEF <40% and/or prior episode of HF

**Procedure related**

Multivessel disease
Multiple stents needed
Left main stenting
Bifurcation stenting
ACC/AHA type B2, C lesion
Venous or arterial coronary graft

**Key Exclusions:** ACS; need for chronic oral anticoagulation; other planned coronary revascularization within 30 days

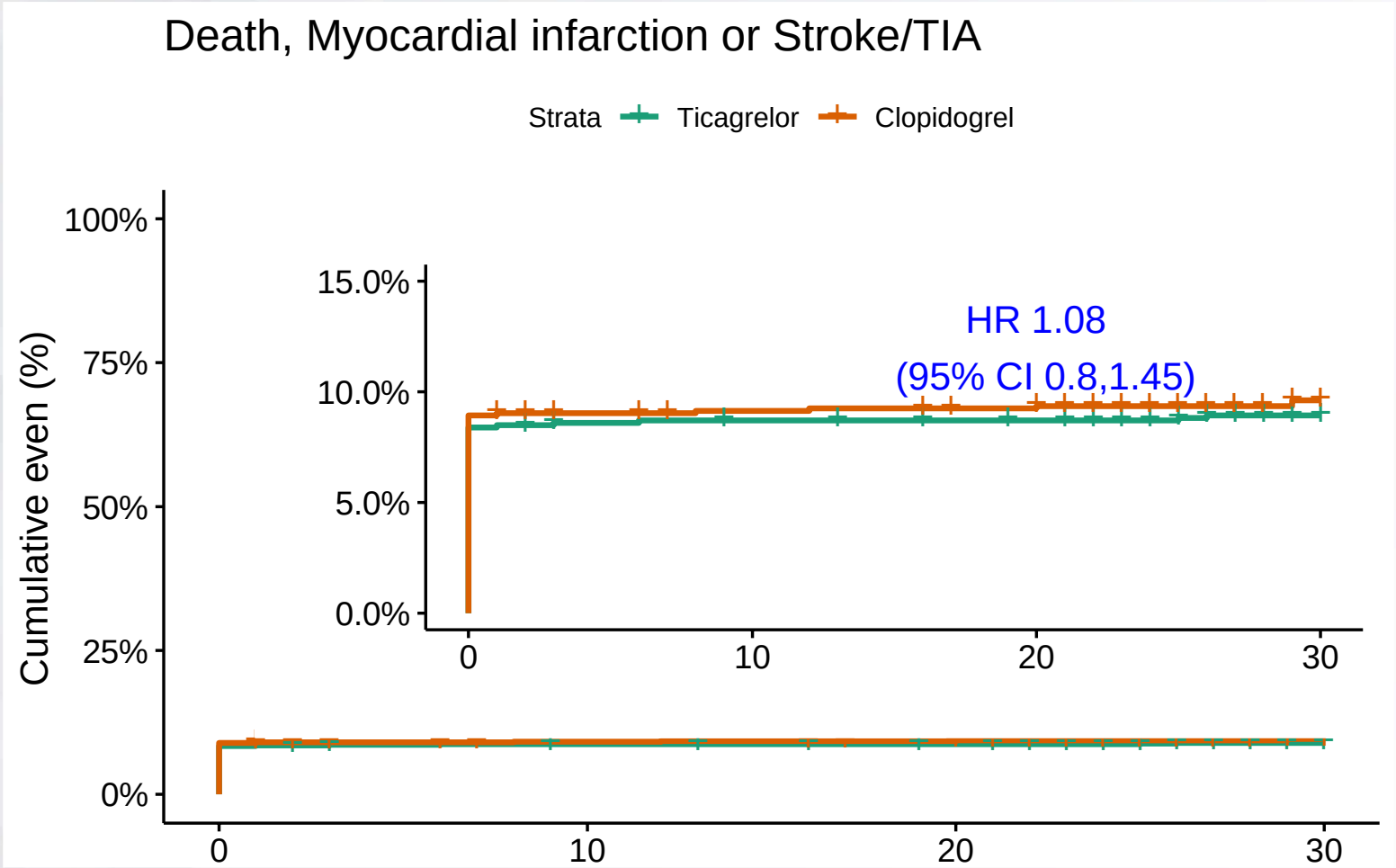
# Primary Outcome




| | N events (%) Ticagrelor | N events (%) Clopidogrel | OR (95% CI) | p value |
|---|---|---|---|---|
| † Primary Outcome | 334/941 (35·5%) | 341/942 (36·2%) | 0·97 (0·80-1·17) | 0·75 |
| Myocardial Infarction (4a) | 80/941 (8·5%) | 77/942 (8·2%) | 1·03 (0·63-1·68) | 0·79 |
| Stent Thrombosis (4b) | 3/941 (0·3%) | 3/942 (0·3%) | 1·00 (0·20-4·97) | 1·00 |
| Major myocardial injury | 251/941 (26·7%) | 261/942 (27·7%) | 0·95 (0·78-1·17) | 0·61 |

†3rd Universal definition of MI
Thygesen K et al. Eur Heart J 2012

# Clinical Outcomes at 30 days




*"**death and stroke/TIA were rare events** (0·2% vs 0% and 0·2% vs 0·1%) in the ticagrelor and clopidogrel group respectively "*


Silvain J. et al. Lancet 2020;396:1737–44

# Safety

| | Ticagrelor N=941 | Clopidogrel N= 942 | OR 95% CI | P value |
|---|---|---|---|---|
| **At 48 hours** | | | | |
| Major Bleeding Events (BARC 3 or 5) | 1 (0·1%) | 0 (0·0%) | - | 0·50 |
| Nuisance or Minor bleeding (BARC 1 or 2) | 63 (6·7%) | 50 (5·3%) | 1·28 (0·87 – 1·88) | 0·20 |
| Any Bleeding (BARC 1 to 5) | 64 (6·8%) | 50 (5·3%) | 1·30 (0·89-1·91) | 0·17 |
| **At 30 days** | | | | |
| Major Bleeding Events (BARC 3 or 5) | 5 (0·5%) | 2 (0·2%) | 2·51 (0·49-13·0) | 0·29 |
| **Nuisance or Minor bleeding (BARC 1 or 2)** | **105 (11·2%)** | **71(7·5%)** | **1·54 (1·12-2·11)** | **0·007** |
| **Any Bleeding (BARC 1 to 5)** | **110 (11·7%)** | **73 (7·7%)** | **1·58 (1·15-2·15)** | **0·0039** |

*Dyspnea was more frequent in the ticagrelor group (11.2%) as compared with the clopidogrel group (0.5%) and lead to more frequent discontinuation of the study drug (2.2% vs. 0.4%) for each group respectively.*

***"Story About Temporal Antithrombotic Tuning"***

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

# Management of Antithrombotic Therapy after Acute Coronary Syndromes

Fatima Rodriguez, M.D., M.P.H., and Robert A. Harrington, M.D.

From the Division of Cardiovascular Medicine, Department of Medicine, and the Stanford Cardiovascular Institute (F.R., R.A.H.), Stanford University, Palo Alto, CA. Address reprint requests to Dr. Harrington at the Department of Medicine, Stanford University, 300 Pasteur Dr., S102, MC:5110, Stanford, CA 94305, or at robert.harrington@stanford.edu.

N Engl J Med 2021;384:452-60.
DOI: 10.1056/NEJMra1607714


BECAUSE OF RAPIDLY CHANGING GUIDELINES IN RESPONSE TO MULTIPLE clinical trials of new therapies, the management of antithrombotic agents for patients after an acute coronary syndrome is becoming increasingly complex. Patients and clinicians must make treatment decisions by weighing the antithrombotic benefits of antiplatelet agents and the anti-ischemic benefits of anticoagulant agents against the risk of bleeding, including severe, life-threatening bleeding. Treatment decisions should be individualized by incorporating additional variables in this risk–benefit assessment, including but not limited to demographic characteristics of the patient, examination findings, laboratory testing, and imaging, as well as the patient's values and preferences.

The pathobiology of acute coronary syndromes is characterized by disruption of coronary atherosclerotic plaque through fissure, erosion, or rupture, resulting in activation of platelets and the coagulation system; the clinical result is myocardial ischemia or infarction, depending on the extent of coronary-artery occlusion.[1,2] Acute coronary syndromes are initially categorized on the basis of the 12-lead electrocardiogram (ECG), with patients separated into two treatme pathways: one for patients with ST-segment elevation (STE) and one for pati without persistent STE. This initial ECG-guided risk stratification drive treatment decisions during hospitalization and is also important for prog

N Engl J Med 2021;384:452-60.

# Story About Temporal Antithrombotic Tuning

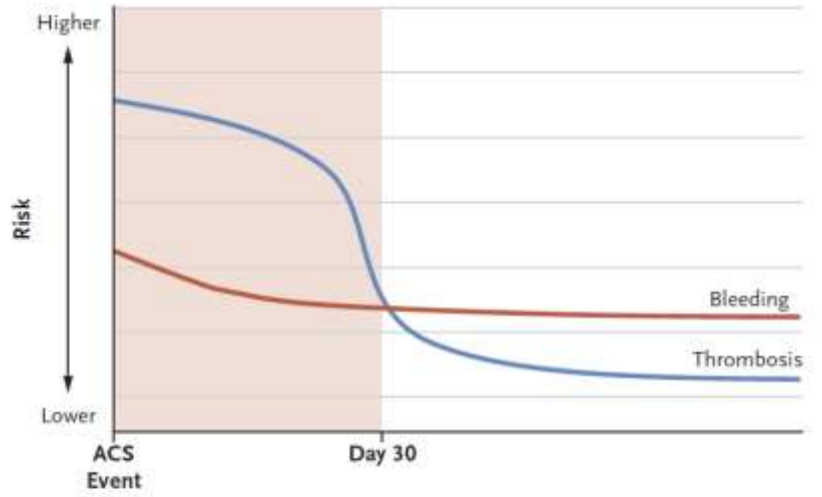



**Figure 1. Risks of Thrombosis and Bleeding after an Acute Coronary Syndrome (ACS).**

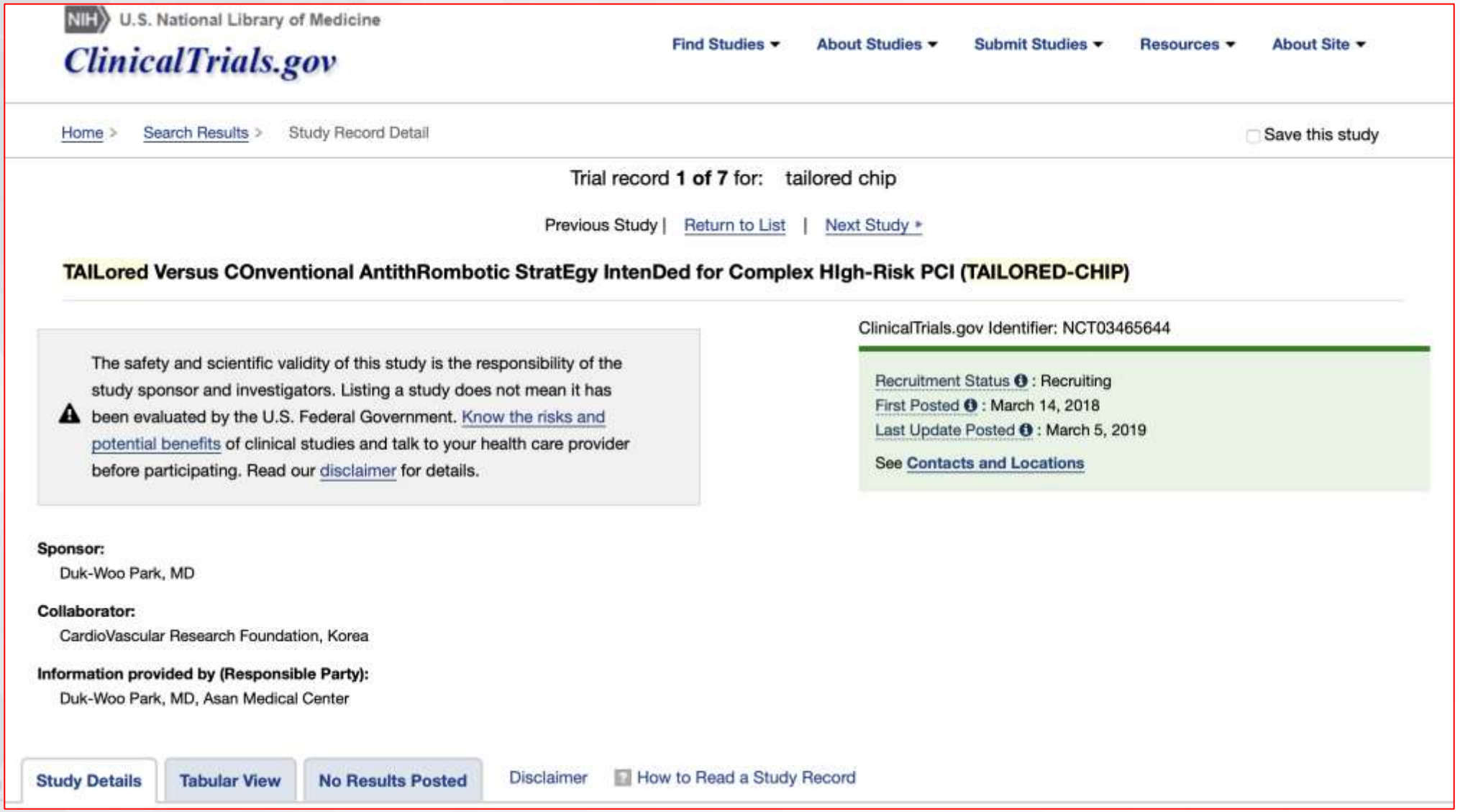
In the first 30 days after an ACS event, the benefits of intensive antithrombotic therapy generally outweigh the increased risk of bleeding. However, this benefit dissipates with additional time after the ACS event, favoring a therapeutic approach that considers the risks of both bleeding and thrombosis.

**Table 2. Suggested Approaches to Antithrombotic Treatment after an ACS Event.***

| Time after ACS Event | Default Strategy | Patients with High Ischemic Risk | Patients with High Bleeding Risk | Patients with Concomitant Atrial Fibrillation† |
|---|---|---|---|---|
| ≤1 mo | Aspirin and newer-generation $P2Y_{12}$ inhibitor | Aspirin and newer-generation $P2Y_{12}$ inhibitor | Aspirin and newer-generation $P2Y_{12}$ inhibitor | Aspirin, clopidogrel, and DOAC‡ |
| >1 mo to 12 mo | Aspirin and newer-generation $P2Y_{12}$ inhibitor | Aspirin and newer-generation $P2Y_{12}$ inhibitor | Any $P2Y_{12}$ inhibitor alone | Clopidogrel and DOAC |
| >12 mo | Any $P2Y_{12}$ inhibitor alone | Aspirin and newer-generation $P2Y_{12}$ inhibitor, or switch to aspirin and low-dose rivaroxaban | Any $P2Y_{12}$ inhibitor or aspirin | DOAC |

N Engl J Med 2021;384:452-60.

# Complex CHIP Population : TAILORED-CHIP Trial



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Trial record **1 of 7** for: tailored chip

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**TAILored Versus COnventional AntithRombotic StratEgy IntenDed for Complex HIgh-Risk PCI (TAILORED-CHIP)**

ClinicalTrials.gov Identifier: NCT03465644

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Recruitment Status : Recruiting
First Posted : March 14, 2018
Last Update Posted : March 5, 2019

See Contacts and Locations

**Sponsor:**
Duk-Woo Park, MD

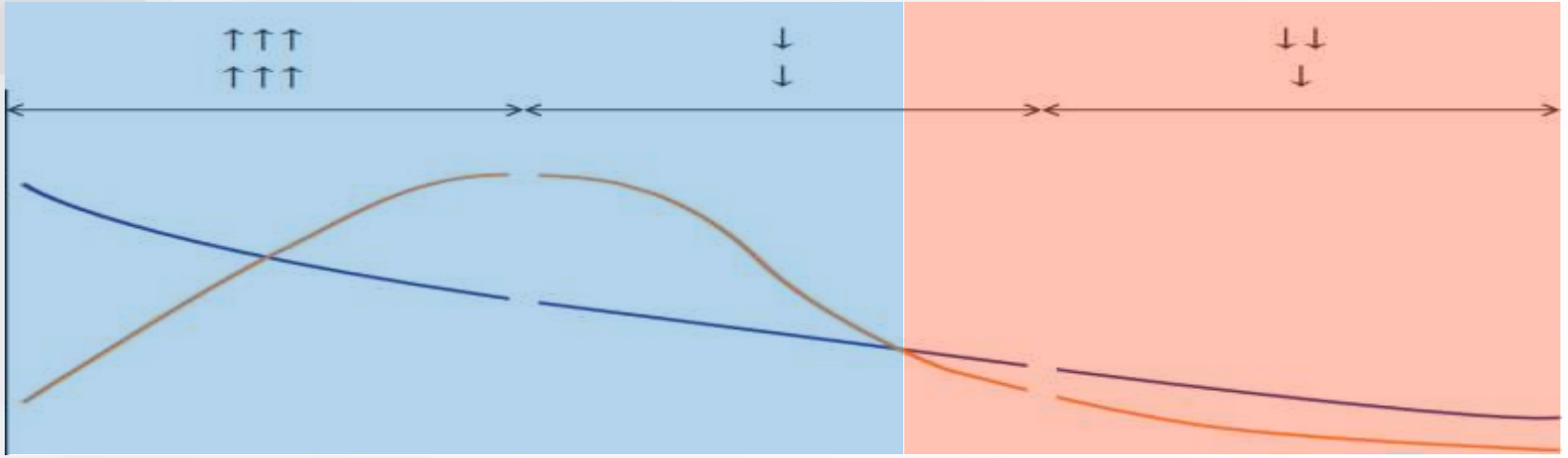
**Collaborator:**
CardioVascular Research Foundation, Korea

**Information provided by (Responsible Party):**
Duk-Woo Park, MD, Asan Medical Center

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

# TAILORED-CHIP Trial:
## Study Hypothesis

**Complex High-risk PCI (CHIP Patients)**

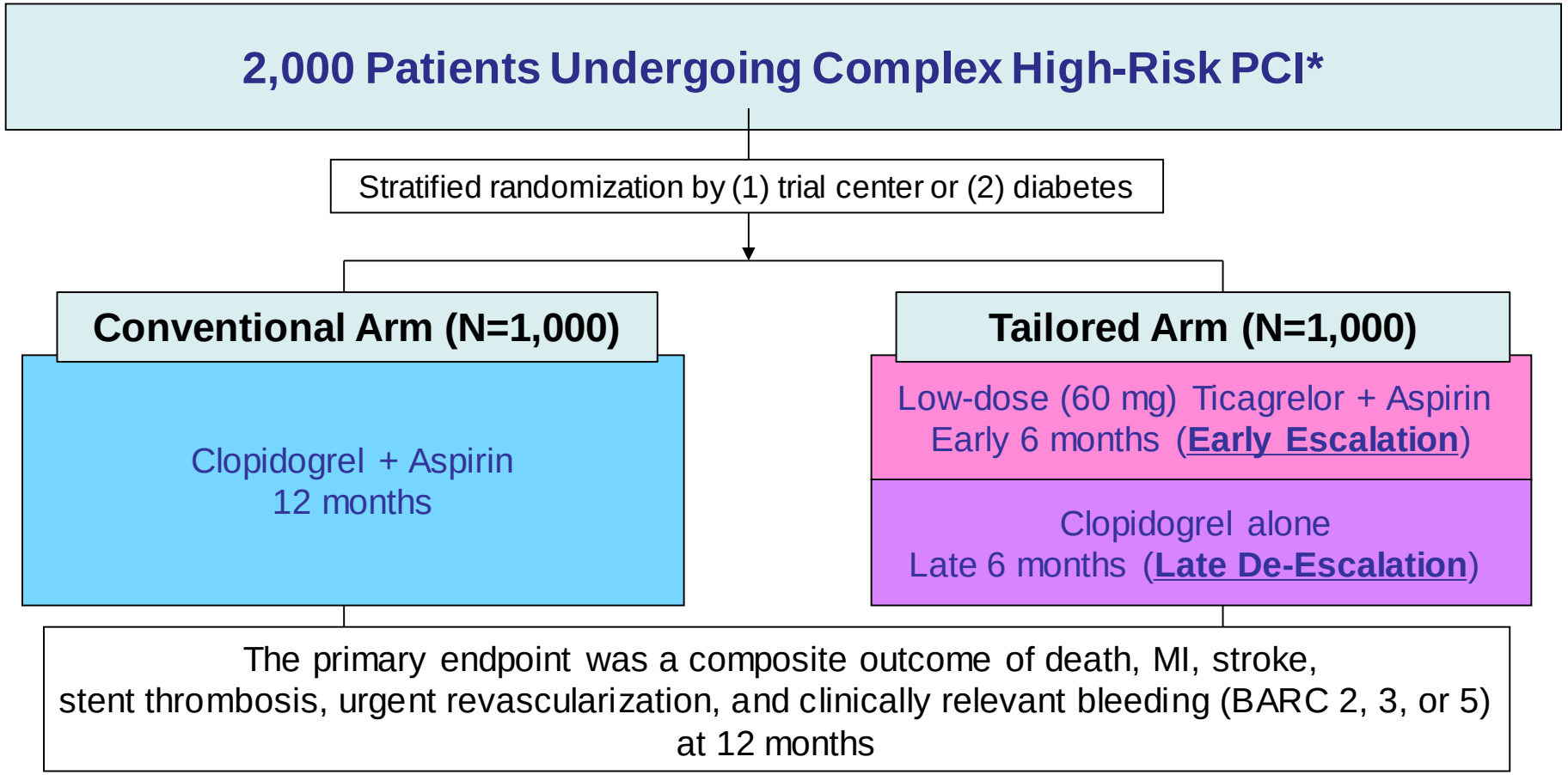



**More Potent Strategy**
**For Early Ischemic Risk**
**"Low-dose Ticagrelor + ASA"**

**Less Potent Strategy**
**For Late Bleeding Risk**
**"Clopidogrel Only"**

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

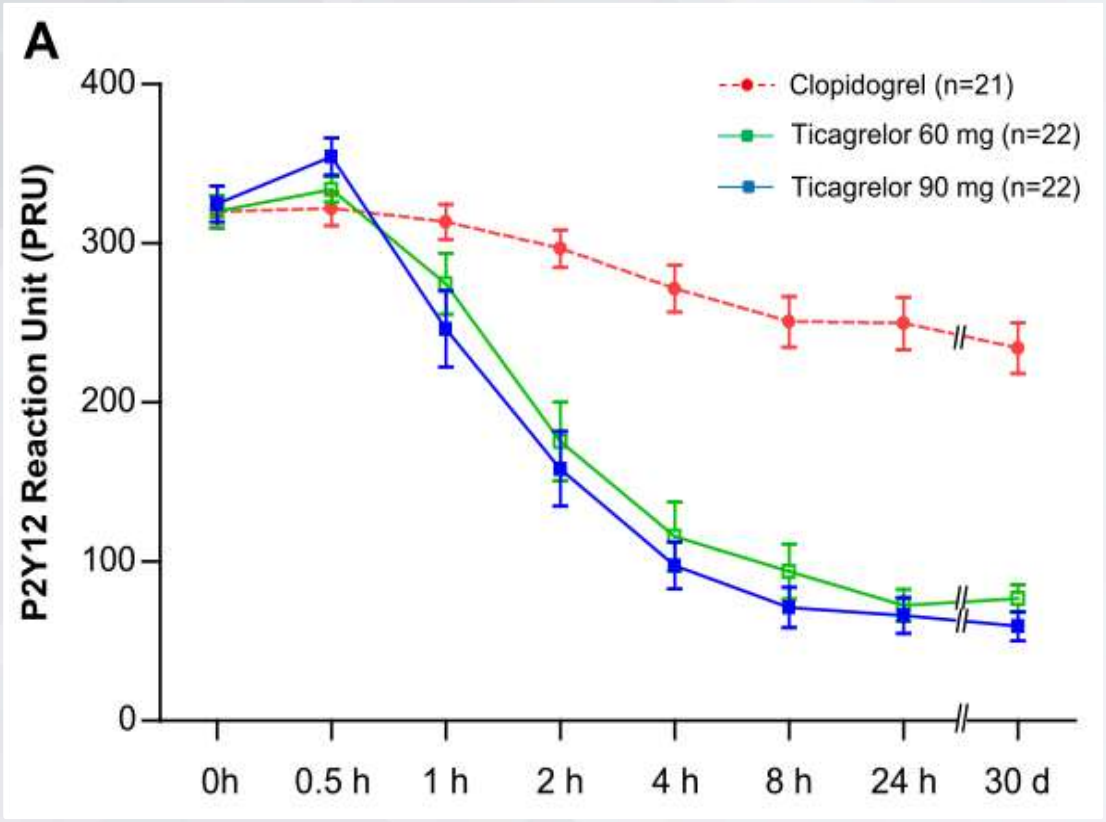
# TAILORED-CHIP Trial

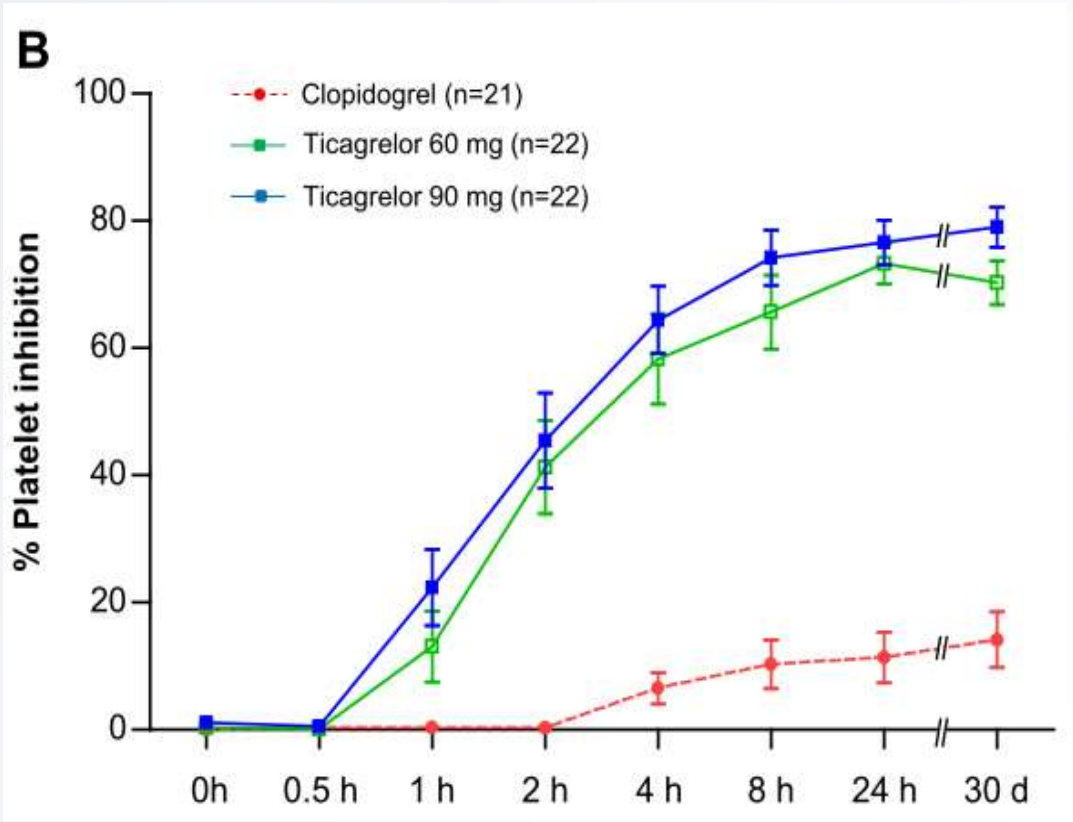



***Complex High-Risk PCI**

: Left main PCI, chronic total occlusion, bifurcation requiring two-stent technique, severe calcification, diffuse long lesion (lesion length ≥ 30mm), multivessel PCI (≥ 2 vessels requiring stent implantation), ≥3 requiring stents implantation, ≥3 lesions will be treated, predicted total stent length for revascularization >60mm, diabetes, CKD (Cr-clearance <60ml/min) or severe LV dysfunction (EF <40%).

# Rationale for Low-Dose Ticagrelor: OPTIMA trial




**Low-dose Ticagrelor > Clopidogrel**

**Low-dose Ticagrelor ≈ Standard-dose Ticagrelor**

DW Park, SJ Park et al, JACC 2018;71:1594-1595.

# Inclusion criteria

- Men or women aged ≥18 years
- Patients undergoing PCI with contemporary newer-generation DES.
- Patients must have at least one of any features of complex high-risk anatomic, procedural and clinical-related factors.
  - ✓**Lesion- or procedure-related factors;** ***Left main*** lesion, **bifurcation lesion** requiring ***two stent technique***, ***CTO*** lesion, severe ***calcification***, ***diffuse long*** lesion (lesion length ≥ at least 30mm), **multi-vessel** PCI (**≥ *2 vessels requiring stent implantation***), ***≥3 requiring stent*** implantation, ***≥3 lesions*** will be treated, or predicted ***total stent length > 60 mm***

  Or

  - ✓**Clinical factors;** ***Diabetes, chronic kidney disease*** (CrCl <60 mL/min), **severe LV dysfunction** (*LVEF<40%*)

# Exclusion criteria

- ***Enzyme-positive ACS*** *(NSTEMI or STEMI)*
- Contraindication to aspirin or P2Y12 inhibitors (ticagrelor or clopidogrel)
- Cardiogenic shock at index admission
- Patients treated with only BMS or balloon angioplasty during index procedure
- ***Need for chronic oral anticoagulation*** (warfarin or NOAC)
- ***Active bleeding or extreme-risk for major bleeding*** (e.g. active PUD, GI pathology with high risk for bleeding, malignancy with high risk for bleeding)

# Study endpoints

## Primary

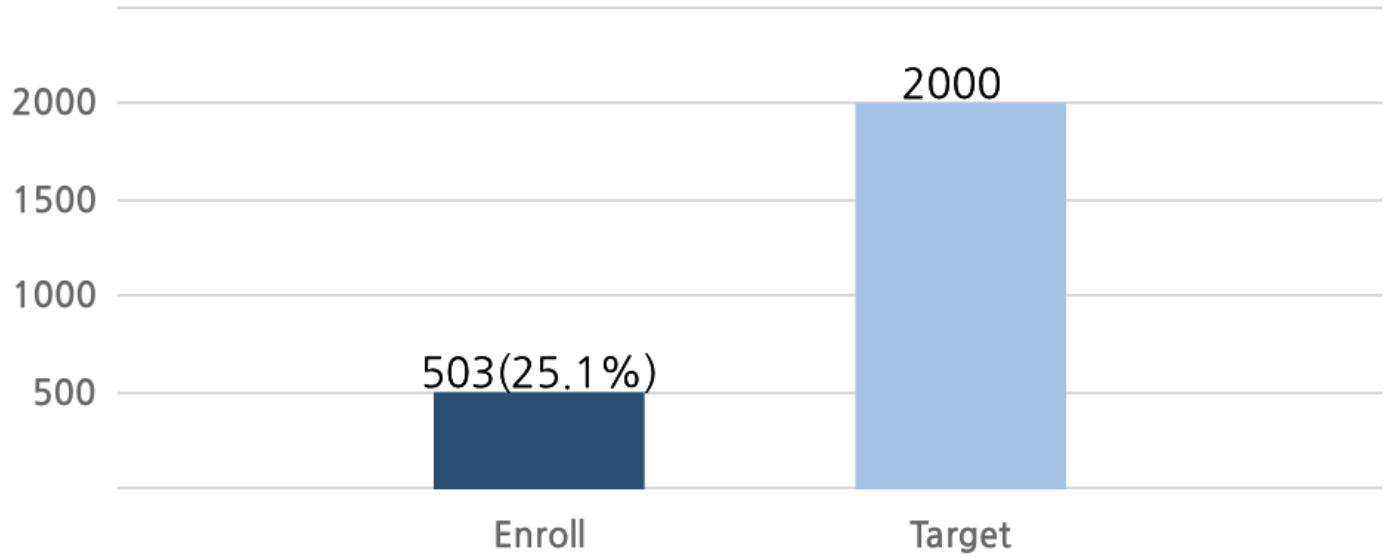
A **net clinical outcome** of all-cause death, MI, stroke, stent thrombosis, urgent revascularization and clinically relevant bleeding (BARC 2,3, or 5) at 12 months post-PCI

## Secondary

- Each component of primary outcome
- Composite of death (all or CV), MI, stroke, stent thrombosis or urgent revascularization
- Composite of death (all or CV), MI, or stroke
- Composite of death (all or CV) or MI
- Any revascularization
- BARC 3 or 5 bleeding
- Major or minor bleeding according to definition from TIMI
- Major or minor bleeding to definition from ISTH

# TAILORED-CHIP Trial Status

## Current Enrollment Status



# Optimal Antithrombotic Strategy in CHIP Population: Summary-I

- Because of rapidly changing guidelines in response to multiple clinical trials of new therapies, the management of antithrombotic agents for patients after ACS or PCI is becoming increasingly complex.
- In the real-world setting, there is no single and simple scenario for optimal antithrombotic strategies for complex CHIP patients.
- Balancing ischemic and bleeding complications after complex CHIP-PCI is an important dilemma for treating clinicians.

# Optimal Antithrombotic Strategy in CHIP Population: Summary-II

- Therapeutic strategies that decouple thrombotic risk from hemorrhagic risk would be required and should be individualized for a tailored, potentially dynamic antithrombotic therapies in patients receiving CHIP-PCI procedures.

- Our **TAILORED-CHIP** trial adapting early escalation and late de-escalation strategy will provide the valuable clinical evidence for management of complex CHIP-PCI patients.