

MHIF FEATURED STUDY: ATTR CM

OPEN and ENROLLING:
EPIC message to *Research MHIF Patient Referral*

CONDITION:

Transthyretin-Mediated
Amyloid Cardiomyopathy

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SPONSOR:

Ionis Pharmaceuticals

DESCRIPTION: A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy

ION-682884 vs. placebo administered by subcutaneous injection once every 4 weeks in patients with ATTR-CM receiving available background therapy. ION-682884 is a ligand-conjugated antisense drug designed to reduce the production of transthyretin to treat all types of TTR amyloidosis.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion

- Amyloid deposits in cardiac or non-cardiac tissue
- Medical history of HF secondary to hereditary or wild-type ATTR-CM

Exclusion

- Cardiomyopathy not primarily caused by ATTR-CM
- Significant co-morbidities
- Current treatment with inotersen, patisiran, diflunisal, doxycycline, non-dihydropyridine calcium-channel blocker

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Creating a world without heart and vascular disease



A 2021 Update on Post PCI Antithrombotic Therapy

Yashasvi Chugh, MD
Interventional Cardiology Fellow



No Disclosures

BALANCING ISCHEMIA & BLEEDING

4 Clinical Scenarios

- **Triple vs Dual** Therapy for PCI in AF
- Anti-thrombotic **therapy 1 year out** from PCI in AF
- **Short DAPT** scenarios
- **Prolonged DAPT** scenarios

Major Bleeding and MI: similar association with mortality in the first year after PCI

More Severe Bleeding equates to greater **Risk of Mortality**

Scenario 1:

My Patient with Atrial Fibrillation had a PCI

WOEST 2013

Design: Open Label, RCT (randomized before or 4h after PCI) Netherlands, Belgium

Duration: 1 year follow up

Primary Outcome:
Any TIMI Bleeding: $P < 0.0001$

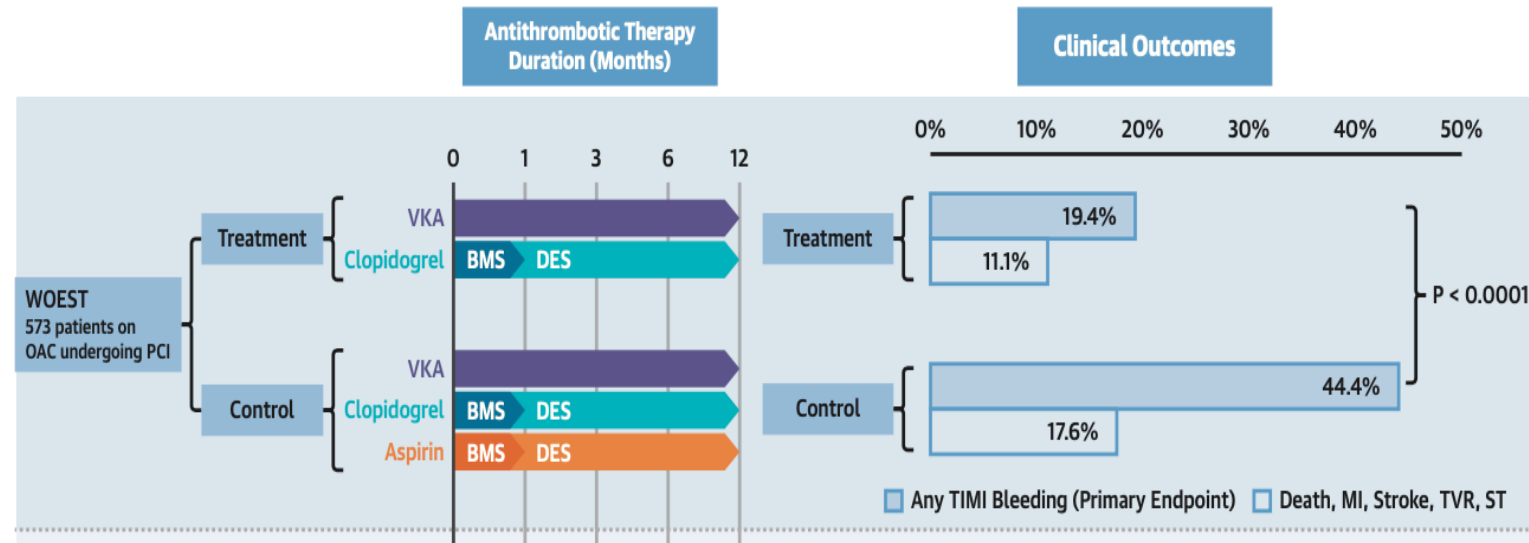
Secondary Outcome:
Combined Death, MI, Revascularization, Stroke, Stent Thrombosis: $P = 0.025$

Limitations: underpowered to detect differences in thrombotic events

ACS vs SIDH: 25% ACS patients

Stent Type: 30% BMS vs 70% DES (in both groups)

ASA: Everyone loaded with 324mg



Stent Thrombosis (any): no significant difference

Dewilde WJM, et al. "Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: An open-label, randomised, controlled trial". *The Lancet*. 2013. 381(9872):1107-1115

After WOEST 2013 we questioned the standard paradigm of Triple Therapy (1 year)

ISAR-TRIPLE 2015

Design: Open Label, RCT, 3 centers Europe

Duration: 9 months

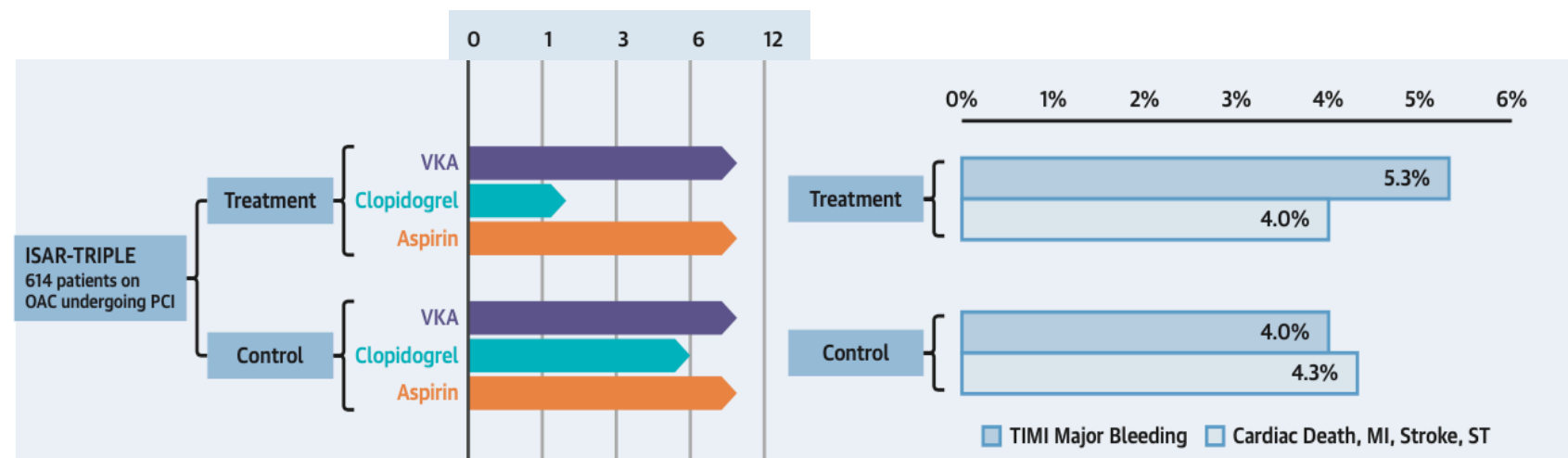
Primary Outcome (Ischemic+Bleeding Events): Net clinical benefit (death, MI, stent thrombosis, stroke, major bleeding): **no difference**

Secondary Outcome (Ischemic Events): Cardiac death, MI, stent thrombosis, or ischemic stroke: **no difference**

Limitations: modest sample size limit power to detect rare outcomes such as stent thrombosis.

ACS vs SIDH: 30% ACS

Stent Type: 0.5% BMS



Stent Thrombosis (any): no significant difference

Fiedler KA et al. "Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation". *J Am Coll Cardiol*. 2015. 65(16):1619-30

ISAR-TRIPLE 2015, Landmark Analysis

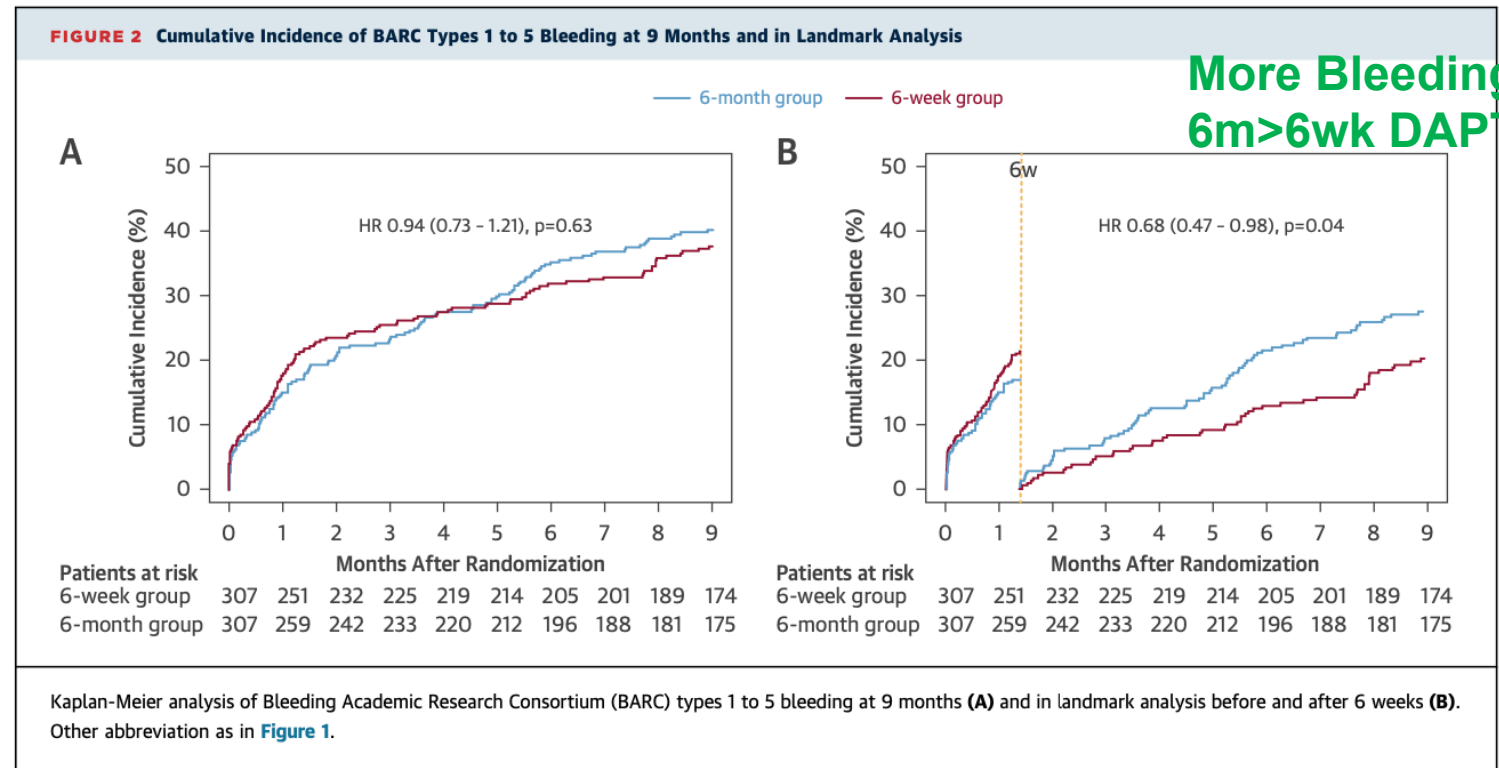
Analysis: 6 weeks vs 6 months of Triple Therapy

Primary Outcome (Ischemic+Bleeding Events): No Difference

Secondary Outcome (Ischemic Events): No Difference

Outcome BARC 1 to 5 Bleeding: More bleeding with Triple

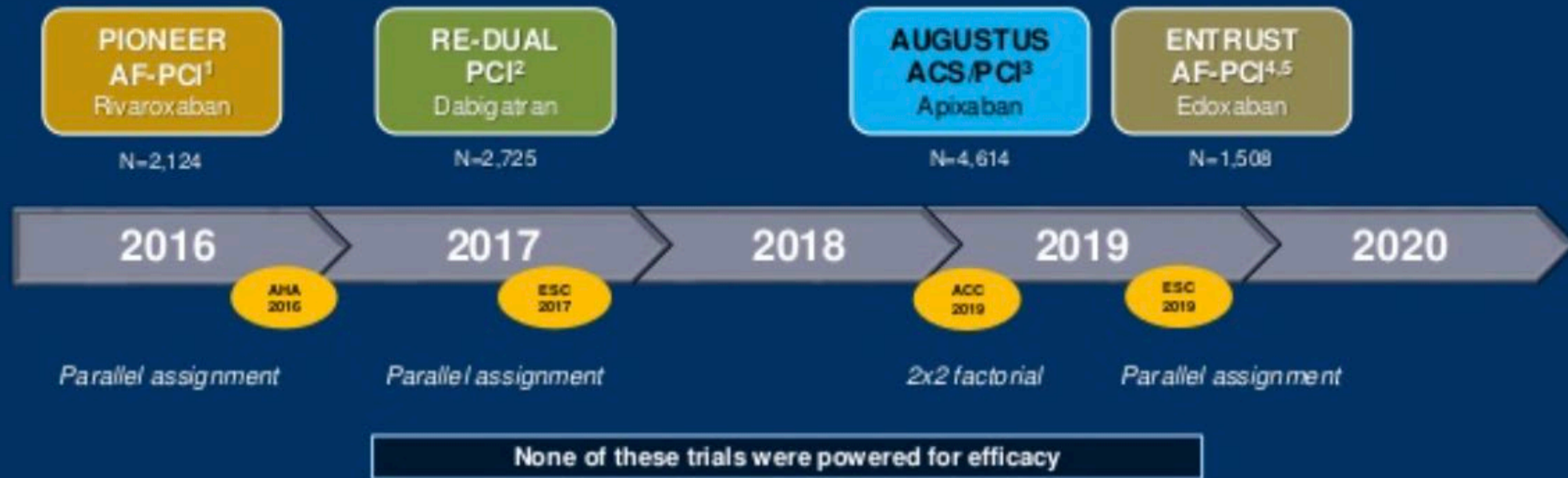
More Bleeding
6m>6wk DAPT



Fiedler KA et al. "Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation". *J Am Coll Cardiol*. 2015. 65(16):1619-30

ISAR TRIIPLE 2015 helped shed light on safety of shorter duration of triple therapy (6 weeks vs 6 months)

What evidence is there for NOACs in AF + ACS?



PIONEER AF-PCI 2016

Design: Open Label, RCT, 26 countries

Duration: 12 months

Primary Outcome: Clinically relevant bleeding

Secondary Outcome: CV death, MI, Stroke

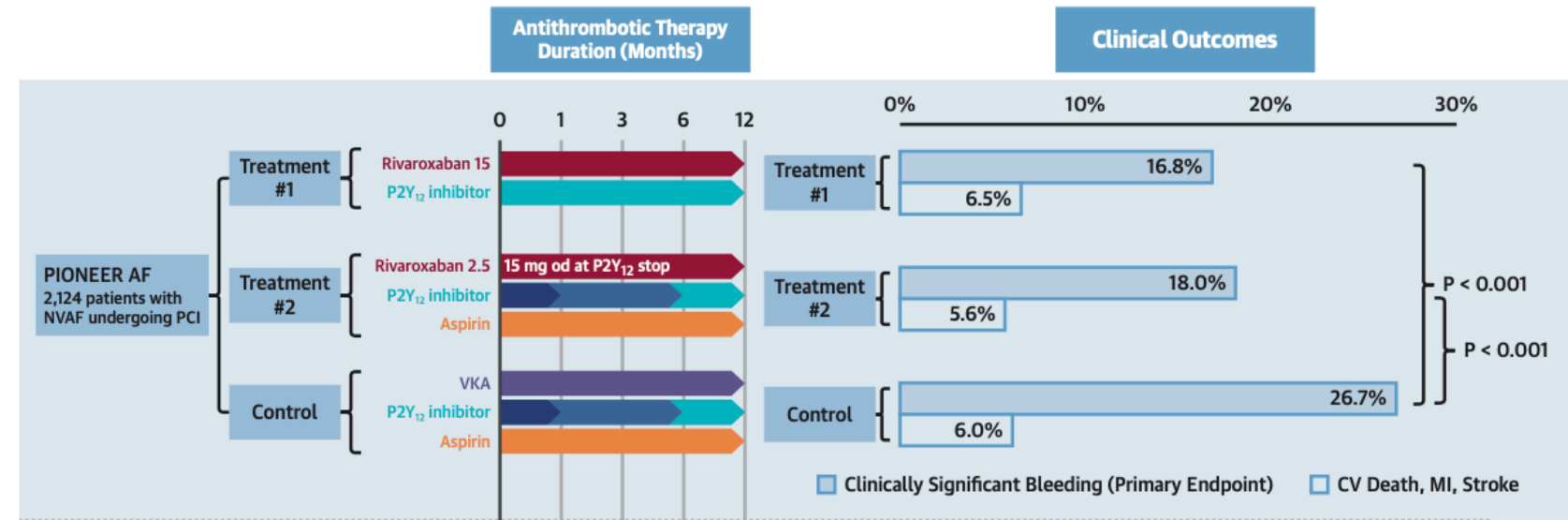
ACS vs SIDH: ACS 51.6% (12% STEMI)

Stent Type: 66% DES

ASA: for 3 days after PCI

2nd Antiplatelet: 96% Plavix

Limitations: Not powered for efficacy, Rivaroxaban dose approved for AF is 20mg/day or 15mg (for renal impairment) vs 15mg/10mg in trial



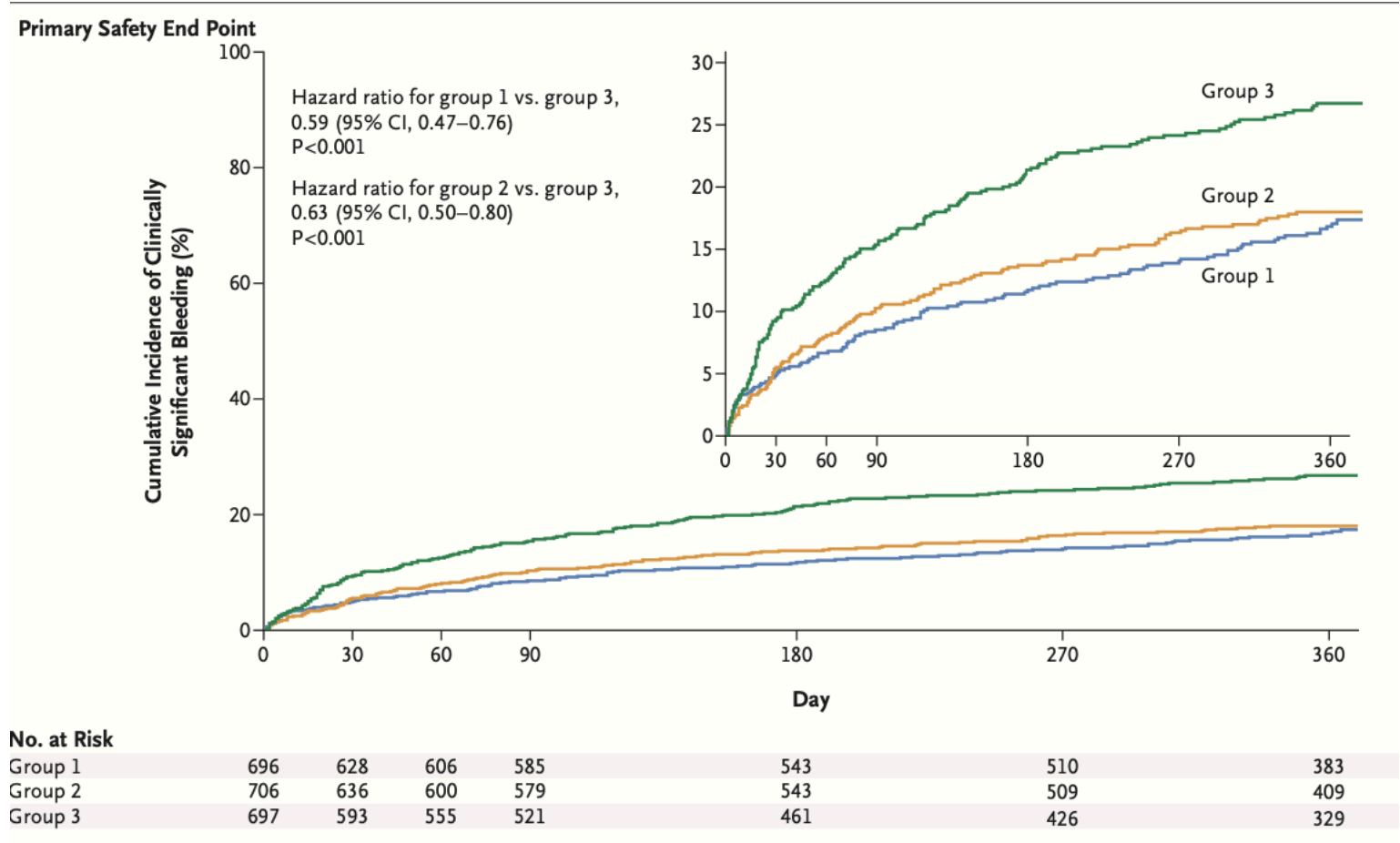
Stent Thrombosis (any): no significant difference

Gibson CM, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med. 2016 Dec 22;375(25):2423-2434

PIONEER AF-PCI 2016

Safety of Rivaroxaban based group > VKA based group

Similar Efficacy



REDUAL-PCI 2017

Design: Open Label, RCT, 41 countries

Duration: 14 months

Primary Outcome: Major or CRNM bleeding through follow-up

Secondary Outcome: Death, MI, Stroke, Systemic Embolism, Unplanned Revascularization (no difference)

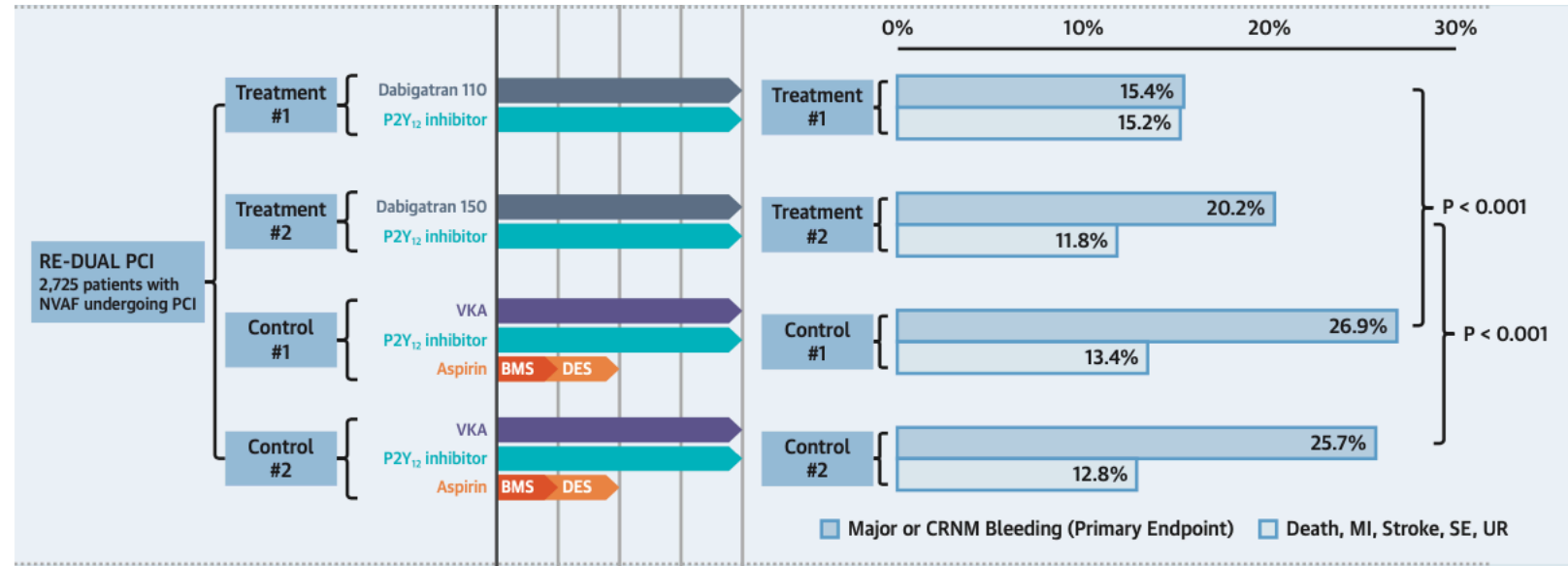
ACS vs SIDH: ACS 50.5% (includes STEMI)

Stent Type: DES 82%

ASA: for 5 days post PCI

2nd Antiplatelet: 88% Plavix

Limitations: Not powered for efficacy

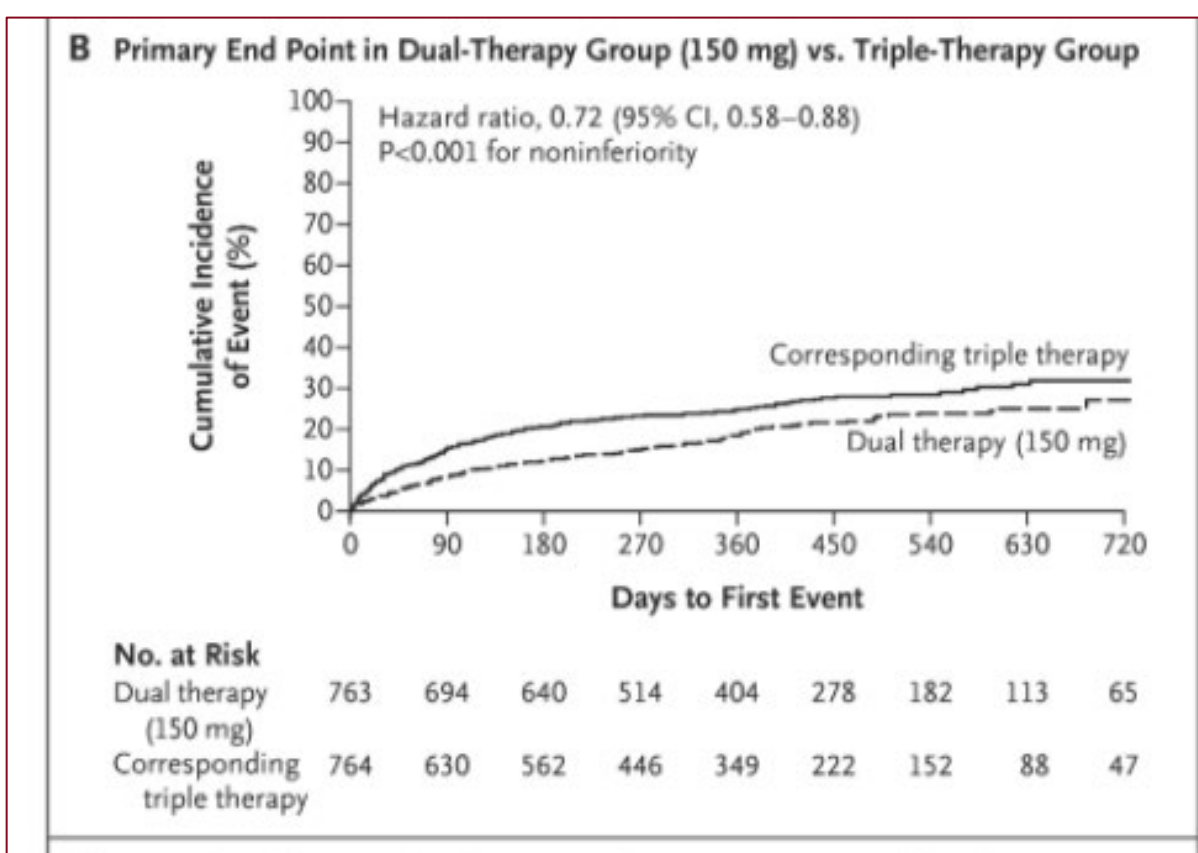
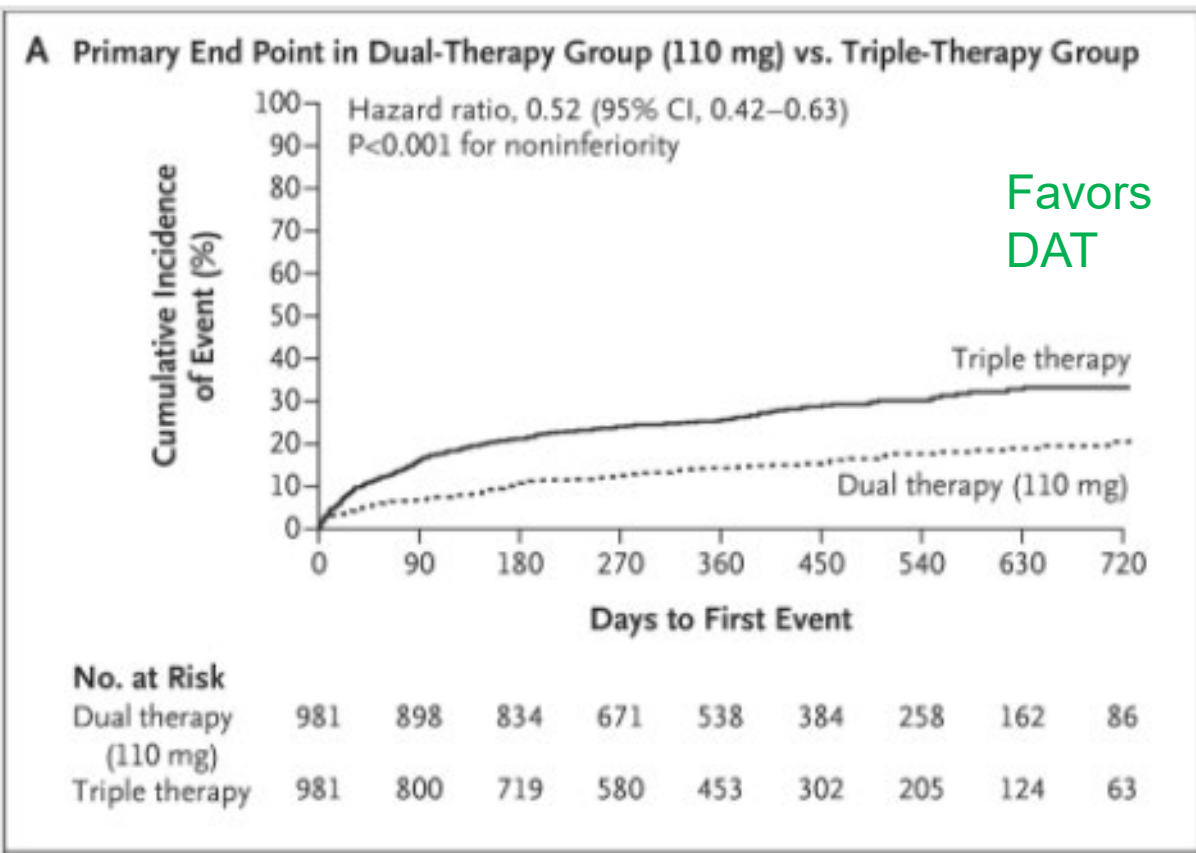


Stent Thrombosis (any): no significant difference

Cannon CP, et al. "Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation". *The New England Journal of Medicine*. 2017. 377(16):1513-1524

REDUAL-PCI 2017

No difference in secondary outcomes



In both these trials, unclear if the low bleeding events were attributed to the use of a DOAC over VKA or to dropping ASA ? (as there was no placebo arm)

AUGUSTUS 2019

Design: Open Label, RCT, 33 countries, placebo controlled

Duration: 6 months

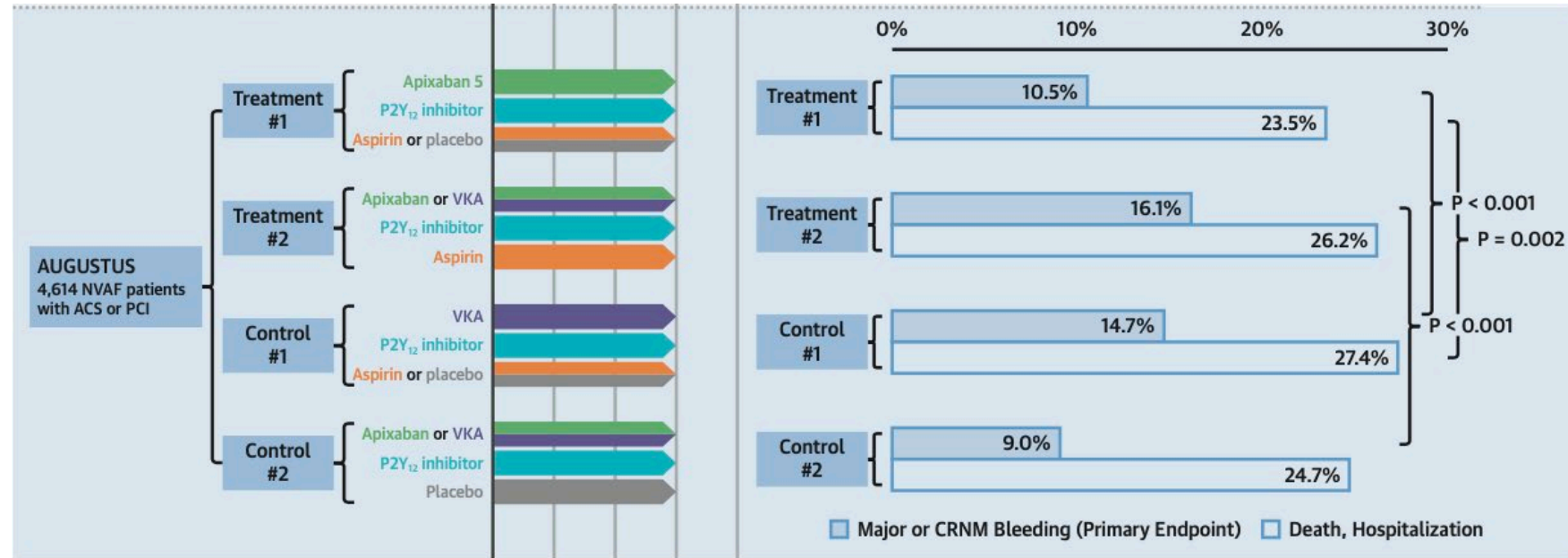
Limitations: Not powered for efficacy

ACS vs SIDH: ACS 38% (includes STEMI)

Stent Type: DES only

ASA: for upto 14 days post PCI

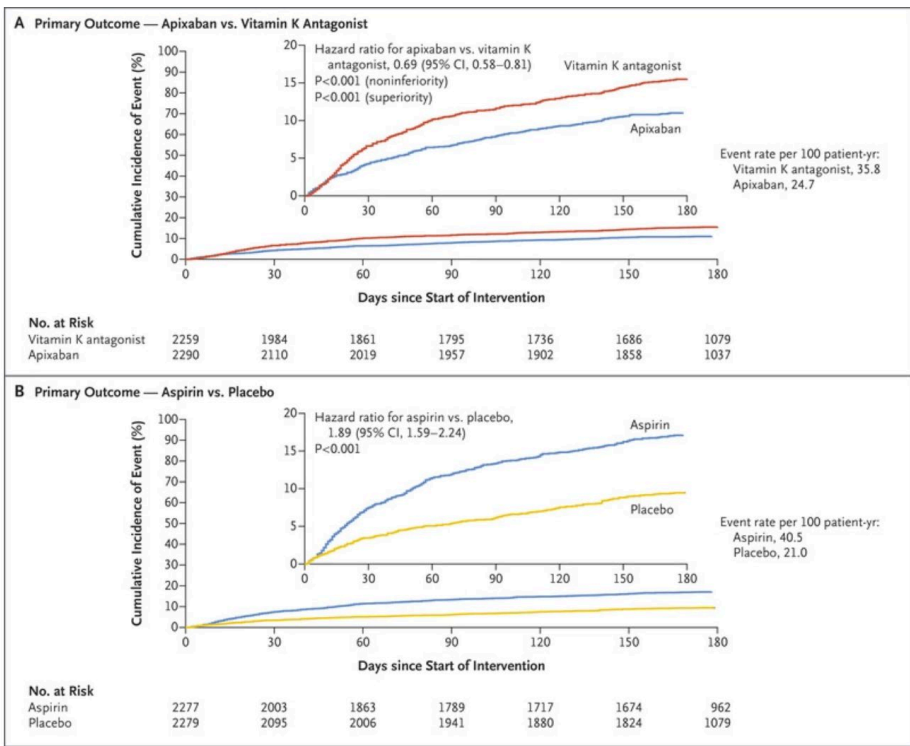
2nd Antiplatelet: 93% Plavix



Stent Thrombosis (any): no significant difference

Lopes RD, et al. "Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation". *The New England Journal of Medicine*. 2019. 380(16):1509-1524.

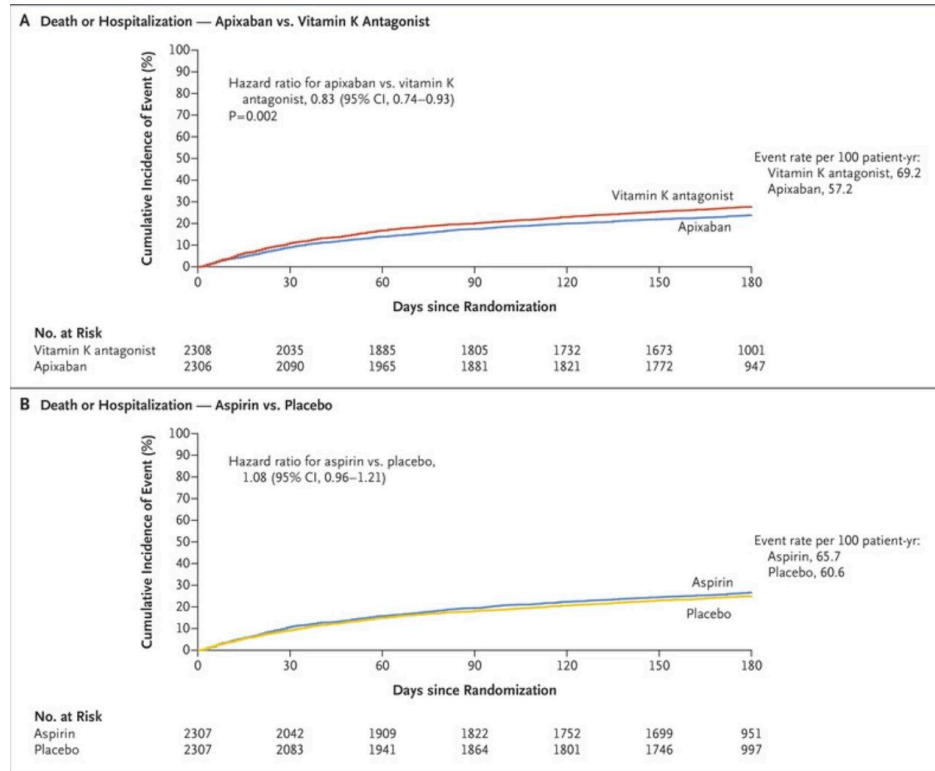
AUGUSTUS 2019



Primary Outcome: Major or CRNM bleeding

RANDOMIZATION 1: Comparisons are apixaban versus warfarin HR 0.69 (95% CI 0.58-0.81); p < 0.001

RANDOMIZATION 2: Comparisons are aspirin versus placebo HR 1.89 (95% CI 1.59-2.24); p < 0.001



Secondary Outcome: Death, Hospitalization

RANDOMIZATION 1: HR 0.83 (95% CI 0.74-0.93); p = 0.002

RANDOMIZATION 2: HR 1.08 (95% CI 0.96-1.21); p = NS

AUGUSTUS helps to disentangle the individual contribution of DOACs and aspirin withdrawal on the risk of bleeding

ENTRUST-AF-PCI 2019

Design: Open Label, RCT

Duration: 12 months

Primary Outcome: Major or CRNM bleeding at 12 months $P=0.001$ for noninferiority

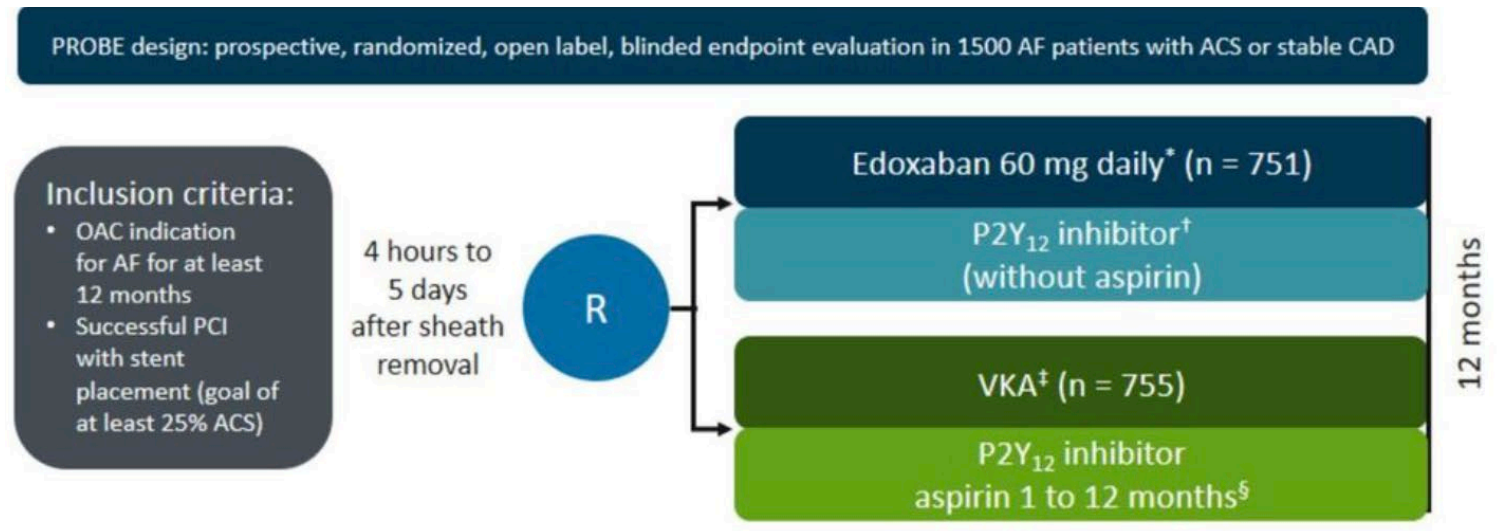
Secondary Outcome: composite CV death, stroke, SEE, MI or definite stent thrombosis ($p = ns$)

ACS vs SIDH: 52% ACS

Stent Type: DES

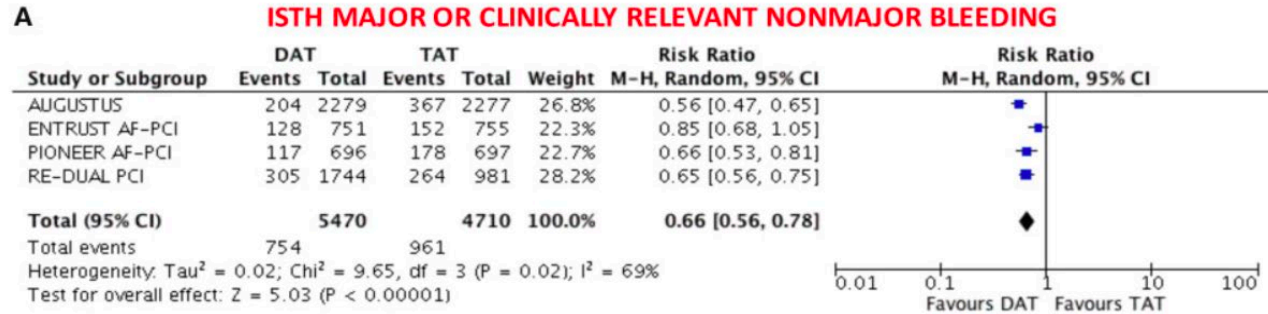
ASA: upto 5 days post PCI

2nd Antiplatelet: 92% Plavix



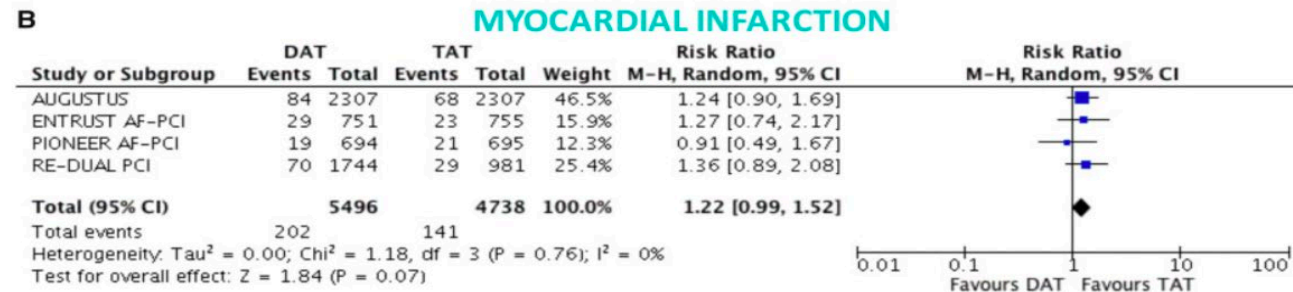
Vranckx P, Lewalter T, Valgimigli M, et al. Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement: rationale and design of the ENTRUST-AF PCI trial. Am Heart J 2018;196: 105–12.

Meta-Analysis 2019

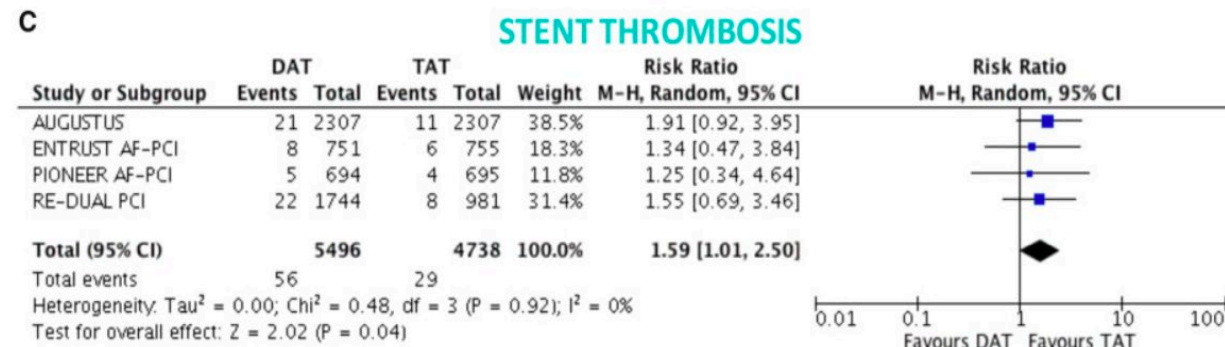


Lower Major Bleeding with DAT

Lower ICH with NOAC based DAT



Increased risk of MI and ST with DAT



European Heart Journal (2019) 40, 3757–3767

Scenario 2:

How do I manage my Patient with Atrial Fibrillation who had PCI >1 year ago

OAC ALONE 2019

Design: Open Label, RCT, 111 sites

OAC (DOAC or VKA) vs OAC + single antiplatelet (ASA or Plavix) 1 year after PCI

Duration: 3 years, 696 patients

Primary Outcome: composite of all-cause death, myocardial infarction, stroke, or systemic embolism

Secondary Outcome: composite of the primary end point and major bleeding

Limitations: Terminated early because of slow enrollment, not powered

ACS vs SIDH: only SIHD

Stent Type: 71% DES

ASA or PLAVIX as Single APT: 86% ASA, 14% PLAVIX

WARFARIN or DOAC: 75% VKA

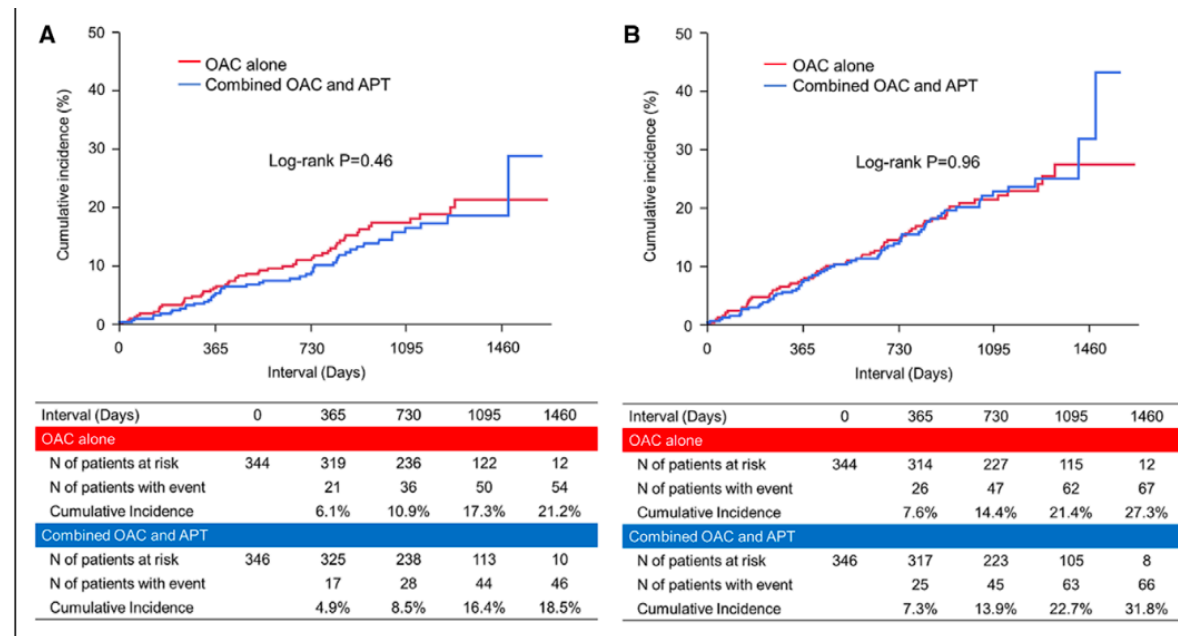


Figure 4. Cumulative incidence of the primary and major secondary end points. A and B, Kaplan–Meier curves showing the cumulative incidence of the primary end point (a composite of all-cause death, myocardial infarction, stroke, or systemic embolism; A), and major secondary end point (a composite of primary end point or major bleeding; B). APT indicates antiplatelet therapy; and OAC, oral anticoagulation.

End Points	OAC Alone		Combined OAC and APT		Hazard Ratio (95% CI)	P Value for Noninferiority	P Value
	(N=344)		(N=346)				
	No. of Patients With Event (Crude Incidence Rate/Annualized Event Rate, %)						
Myocardial infarction	8	(2.3/0.93)	4	(1.2/0.46)	2.03 (0.64–7.59)		0.23
Stent thrombosis	2	(0.58/0.23)	0	(0.0/0.0)	NA*		0.15†

AFIRE 2019

Design: Open Label, RCT, Japan

Rivaroxaban vs Rivaroxaban + single antiplatelet (ASA or P2Y12) 1 year after PCI or CABG in AF patients

Duration: 24 months

OAC >> OAC+APT

Efficacy Outcome: composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause

Safety Outcome: safety end point was major bleeding (ISTH)

Limitations: Rivaroxaban dose based on approval in Japan (10 mg or 15 mg once daily) vs (15mg/20 mg elsewhere)

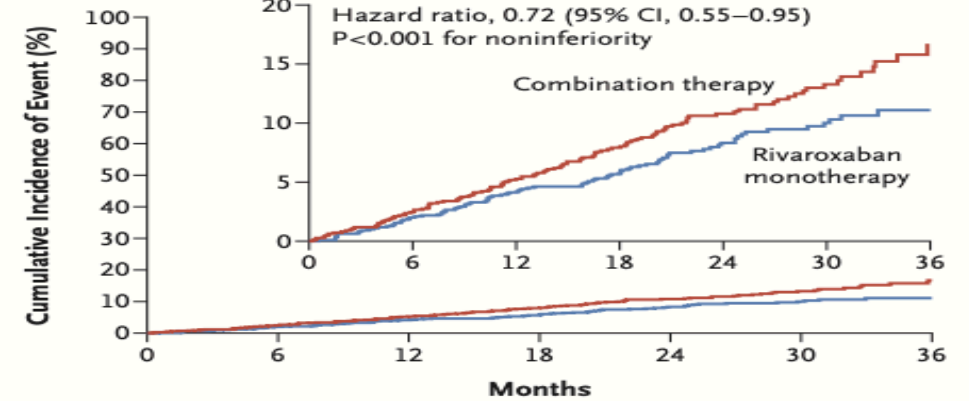
Terminated Early, Increase Mortality in DAT

ACS vs SIDH: SIHD only

Stent Type: 70% DES

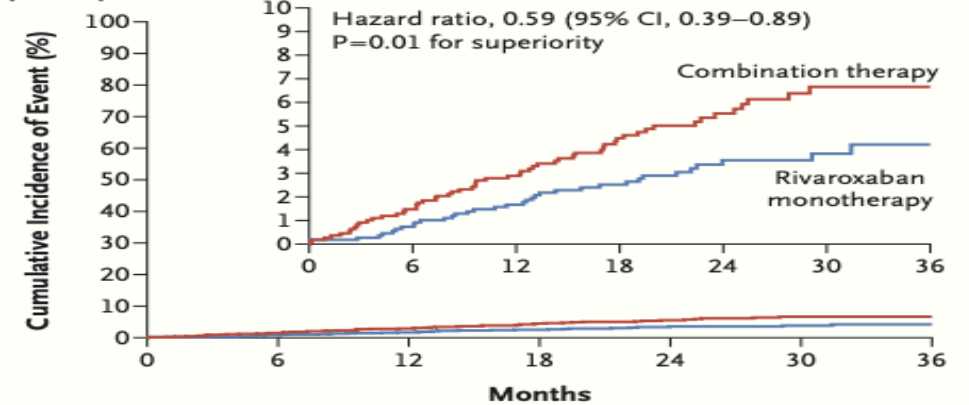
ASA or PLAVIX as Single APT: ASA 70%

A Primary Efficacy End Point



No. at Risk	0	6	12	18	24	30	36
Combination therapy	1108	1057	962	754	499	292	80
Rivaroxaban monotherapy	1107	1071	984	774	518	309	89

B Primary Safety End Point



No. at Risk	0	6	12	18	24	30	36
Combination therapy	1099	1055	962	750	506	294	80
Rivaroxaban monotherapy	1099	1074	994	786	526	312	89

North American Expert Consensus, 2021

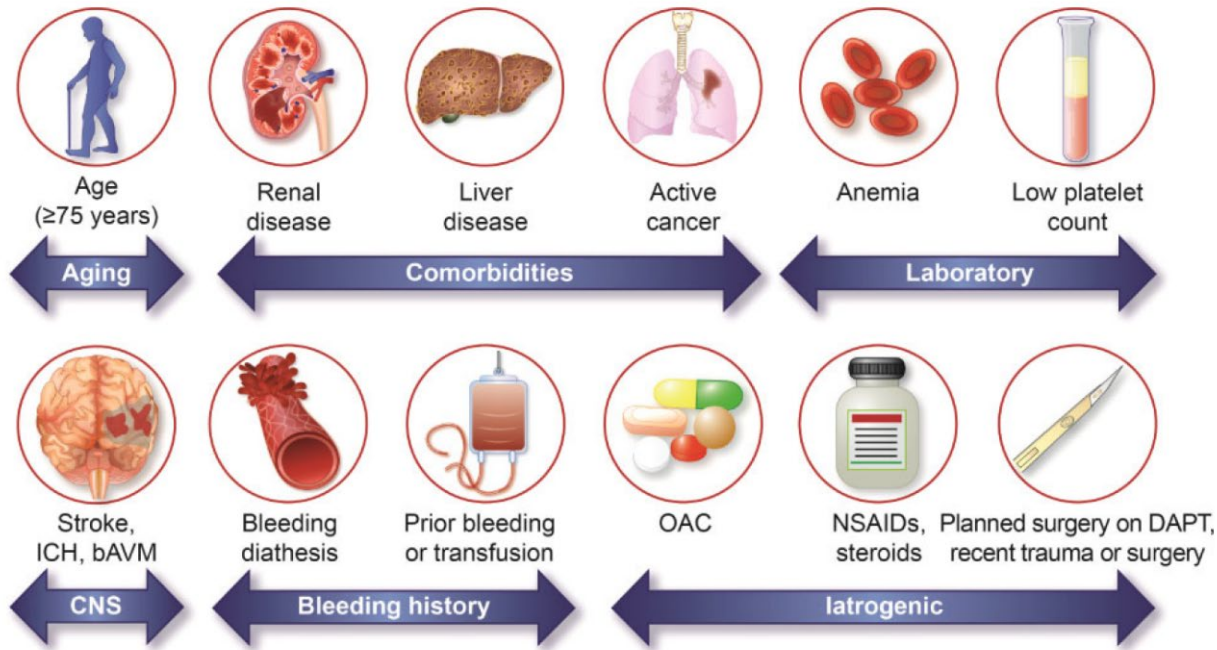


Figure Factors associated with an increased bleeding risk after percutaneous coronary intervention. bAVM indicates brain arteriovenous malformation; CNS, central nervous system; DAPT, dual antiplatelet treatment; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; and OAC, oral anticoagulation.

1 Major or 2 Minor

Table 3. Definition of High Bleeding Risk According to Academic Research Consortium Criteria

Major	Minor
Anticipated use of long-term oral anti-coagulation*	Age ≥75 years
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30 to 59 mL/min)
Hemoglobin <11 g/dL	Hemoglobin 11 to 12.9 g/dL for men and 11 to 11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion
Moderate or severe baseline thrombocytopenia† (platelet count <100×10 ⁹ /L)	Long-term use of oral NSAIDs or steroids
Chronic bleeding diathesis	Any ischemic stroke at any time not meeting the major criterion
Liver cirrhosis with portal hypertension	—
Active malignancy‡ (excluding non-melanoma skin cancer) within the past 12 months	—
Previous spontaneous ICH (at any time)	—
Previous traumatic ICH within the past 12 months	—
Presence of a bAVM	—
Moderate or severe ischemic stroke§ within the past 6 months	—
Nondeferrable major surgery on DAPT	—
Recent major surgery or major trauma within 30 days before PCI	—

Adapted from Urban et al¹⁰ with permission. bAVM indicates brain arteriovenous malformation; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; and PCI, percutaneous coronary intervention.

*Excludes vascular protection doses.

†Baseline thrombocytopenia is defined as thrombocytopenia before PCI.

‡Active malignancy is defined as diagnosis within 12 months or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

§National Institutes of Health Stroke Scale score ≥5.

Table 4. Definition of High Thrombotic and Ischemic Risk

High thrombotic risk (early events)	High ischemic risk (long-term events)
Acute coronary syndrome	Previous myocardial infarction
Previous stent thrombosis while on antiplatelet treatment	Multivessel coronary artery disease
PCI complexity	Polyvascular disease
3 vessels treated	Diabetes mellitus
≥3 stents implanted	Chronic kidney disease
≥3 lesions treated	Heart failure
Bifurcation with 2 stents implanted	
Total stent length >60 mm	
Surgical bypass graft PCI	
Chronic total occlusion PCI	
Atherectomy device use	
Left main PCI	

PCI indicates percutaneous coronary intervention.

AF patients undergoing PCI—2021 North American Consensus

Time from PCI	Default strategy	Patients at high ischemic/thrombotic and low bleeding risk	Patients at low ischemic/thrombotic or high bleeding risk
Peri-PCI	Triple Therapy (OAC + DAPT)	Triple Therapy (OAC + DAPT)	Triple Therapy (OAC + DAPT)
1 month	Double Therapy up to 12 months (OAC + P2Y ₁₂ inhibitor)	Triple Therapy up to 1 month (OAC + DAPT)	Double Therapy up to 6 months (OAC + P2Y ₁₂ inhibitor)
3 months		Double Therapy up to 12 months (OAC + P2Y ₁₂ inhibitor)	
6 months			
12 months	OAC alone	OAC alone	OAC alone

Peri-PCI period: inpatient stay until time of discharge or a few days longer, up to 1 week post-PCI.
 OAC: prefer a NOAC over VKA if no contraindications.
 Clopidogrel is the P2Y₁₂ inhibitor of choice; ticagrelor may be considered in patients at high thrombotic and acceptable bleeding risks; avoid prasugrel.
 Continuation of antiplatelet therapy in adjunct to OAC beyond one-year should be considered only for select patients with high risk for ischemic recurrences and low bleeding risk.

Circulation. 2021;143:583–596.

One Month of ASA

MHIF Cardiovascular Grand Rounds | May 3, 2021

ASA vs PLACEBO

< 30d More Bleeding but less ischemic events

>30d More Bleeding, no difference in ischemic events

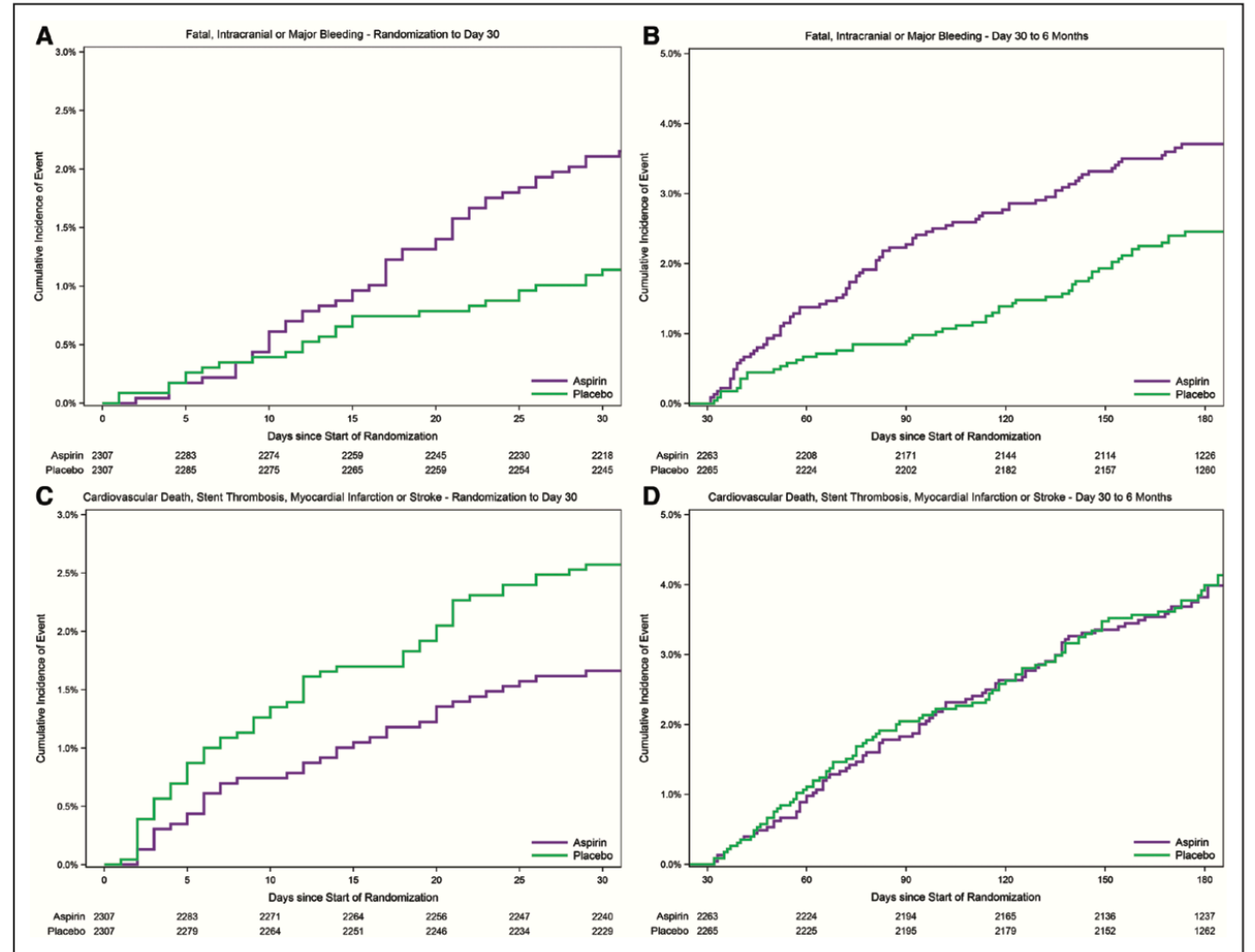
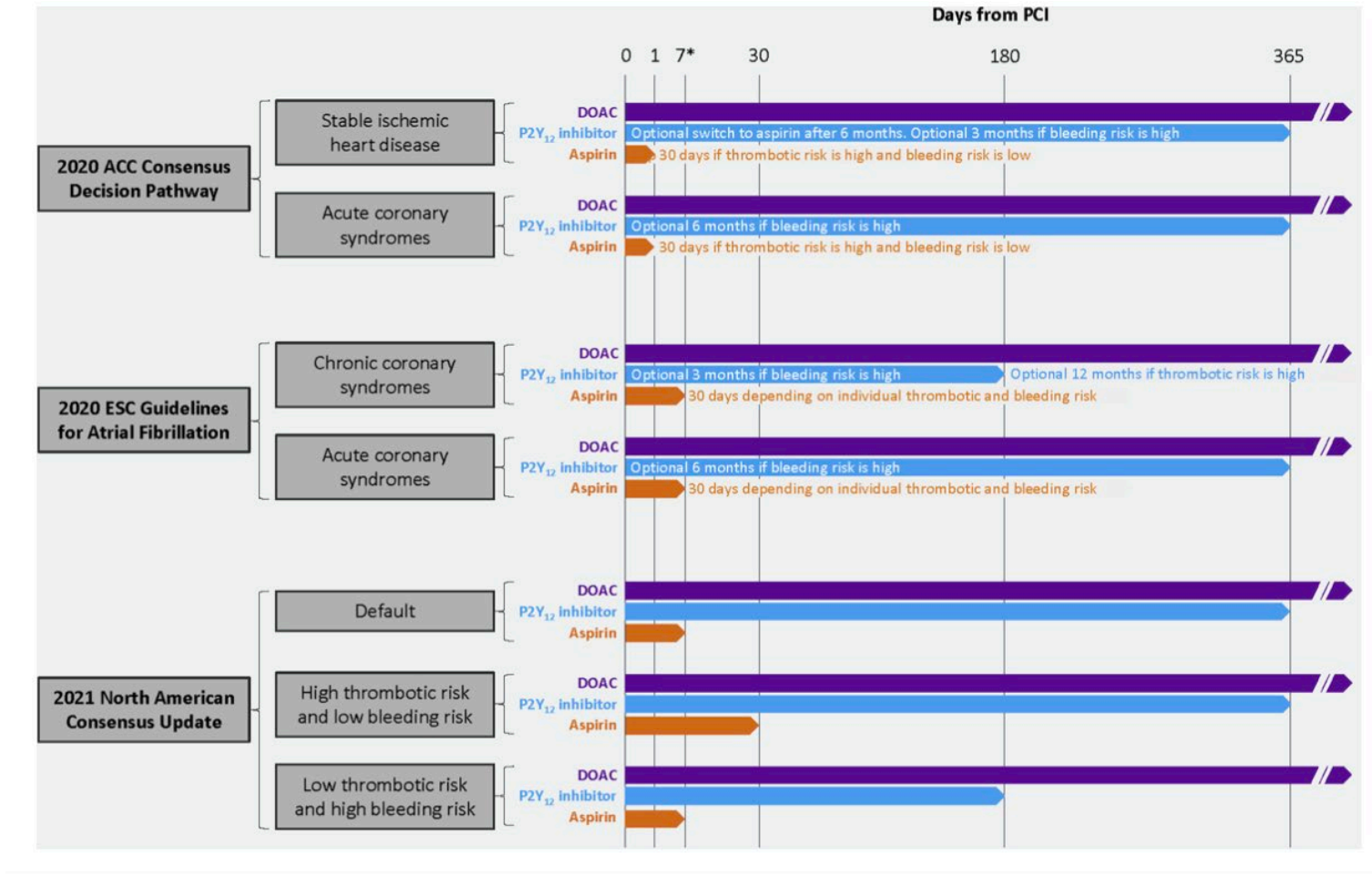


Figure. The risk/benefit tradeoff of aspirin over time.

Kaplan-Meier curves comparing aspirin and placebo for fatal, intracranial, or major bleeding (severe bleeding) from randomization to 30 days (A) and from 30 days to 6 months (B) and for cardiovascular death, stent thrombosis, myocardial infarction, or stroke (severe ischemic events) from randomization to 30 days (C) and from 30 days to 6 months (D). The y axis from randomization to 30 days goes from 0% to 3% and from 30 days to 6 months from 0% to 5%, reflecting the larger absolute number of events between 30 days to 6 months than randomization to 30 days.

Alexander JH, Wojdyla D, Vora AN, Thomas L, Granger CB, Goodman SG, Aronson R, Windecker S, Mehran R, Lopes RD. Risk/benefit tradeoff of antithrombotic therapy in patients with atrial fibrillation early and late after an acute coronary syndrome or percutaneous coronary intervention: insights from AUGUSTUS. *Circulation*. 2020;141:1618–1627. doi: 10.1161/CIRCULATIONAHA.120.046534

ESC 2020 and ACC 2020 Guidelines



JACC: CARDIOVASCULAR INTERVENTIONS VOL. 14, NO. 7, 2021

Choosing The Right DOAC

AF+PCI Trial

NVAF Trial

VTE Trial

Renal Dysfunction

Apixaban

5mg BID or 2.5mg BID

5mg BID

10mg BIDx7d,
5mg BID

2.5 mg BID if 2/3 i)
Age>80y (ii) Cr>1.5
(iii) Wt<60kg
ESRD+

Dabigatran

150mg BID and
110mg BID

150mg BID and
110mg BID

**5-10d parenteral
AC**, then 150mg
BID

75mg BID if
CrCL15-30ml/min

Edoxaban

60mg Daily and
30mg daily

60mg Daily

**5-10d parenteral
AC**, then 60mg
daily

30mg Daily, if
CrCL15-50ml/min

Rivaroxaban

15mg Daily, 10mg
if CrCl 30-50

20mg Daily

15mg BIDx21d,
20mg daily

15mg Daily, if
CrCL15-50ml/min

NOAC>VKA

PLAVIX best for DAT or TAT

ASA therapy during Hospital Stay followed by DAT

Know your thrombotic and bleeding risks

OAC alone at 1 year

Scenario 3:

My patient has a NSTEMI and needs surgery for her Breast Cancer ASAP

DILEMMA

Which Stent?: BMS, DES (New Gen)

DAPT Duration?

SAPT after DAPT with ASA or P2Y12i?

Evolution of DAPT

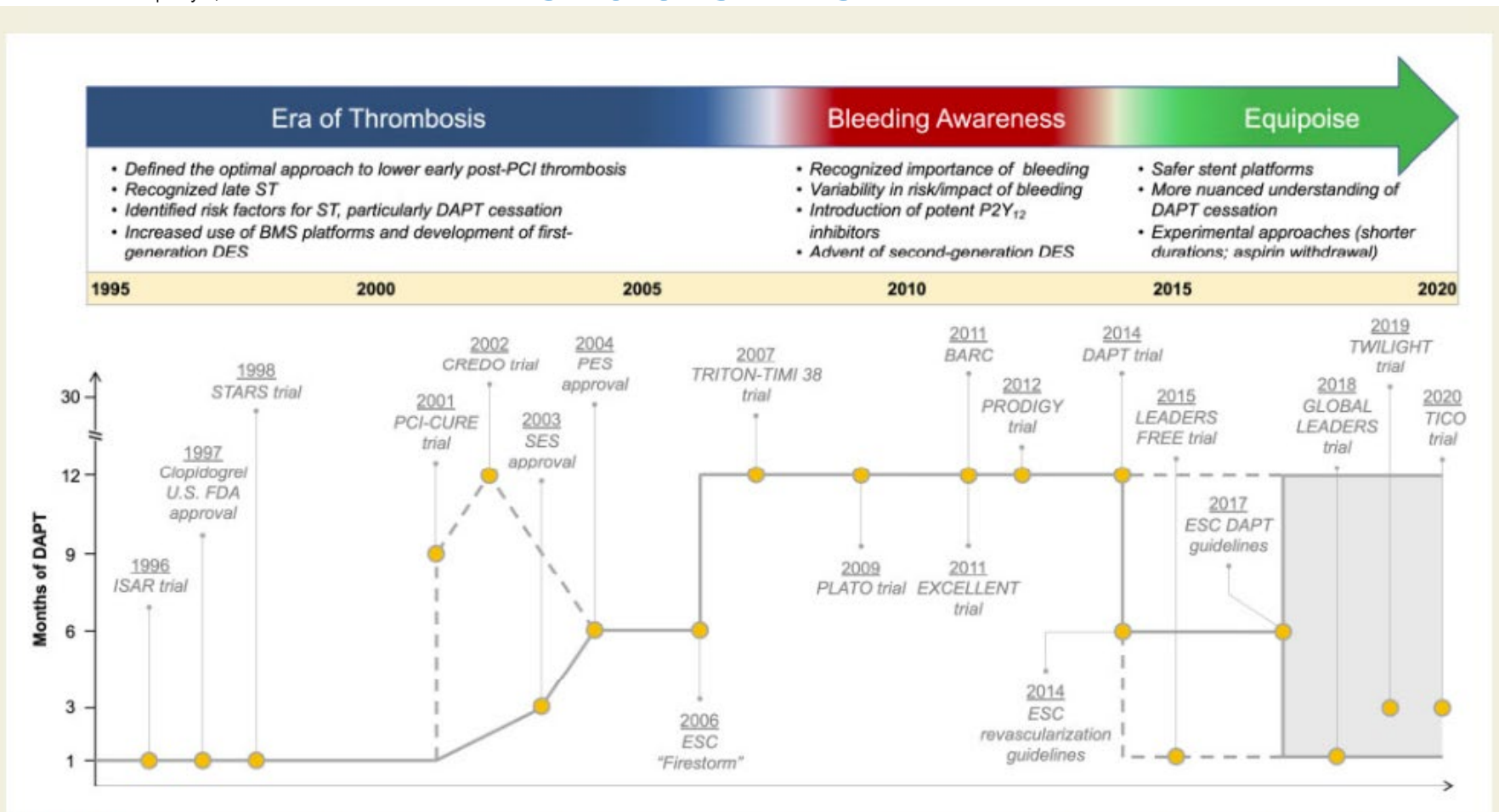
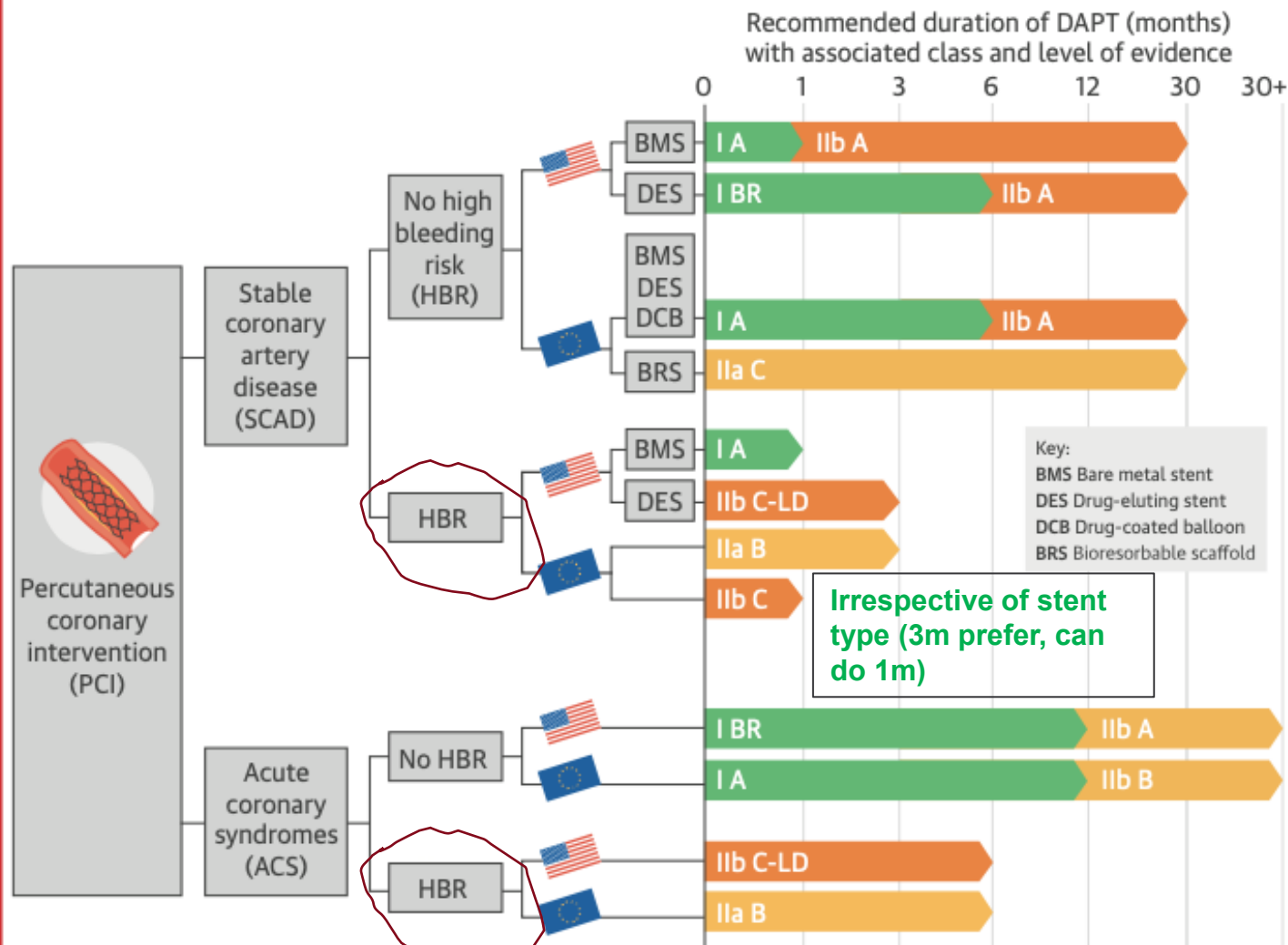


Figure 2 Evolving duration of antiplatelet therapy after percutaneous coronary intervention. BARC, Bleeding Academic Research Consortium; BMS, bare metal stents; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ST, stent thrombosis; U.S. FDA, United States Food and Drug Administration.

European Heart Journal (2021) 42, 339–351

ACC/AHA 2016, ESC 2017 GUIDELINES ON DAPT

CENTRAL ILLUSTRATION Recommendations for Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention



Capodanno, D. et al. J Am Coll Cardiol. 2018;72(23):2915-31.

DILEMMA

Which Stent?: BMS, DES (New Gen)

LEADERS FREE 2015

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Design: DCS (Biofreedom: Polymer Free Umirolimus coated stent) vs BMS, 1:1 randomization, double blind, High bleeding risk patients

Duration: 390 days, 2466 patients

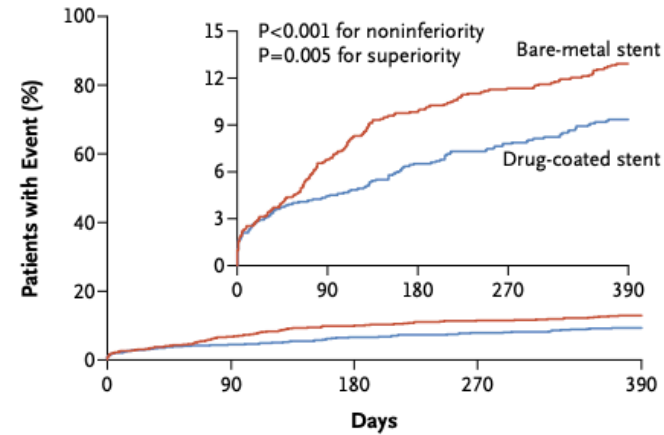
Primary Safety Outcome: composite of cardiac death, MI, ST

Secondary Efficacy Outcome: TLR

DAPT Duration: 1 month (ASA, PLAVIX) followed by ASA

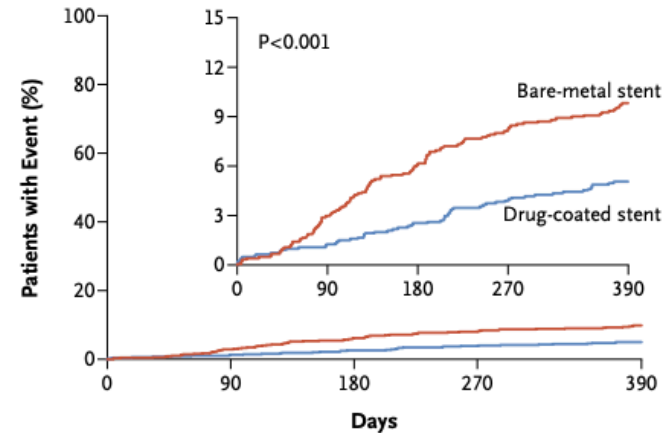
SIHD/ACS: 59% SIHD

A Primary Safety End Point



No. at Risk	0	90	180	270	390
Drug-coated stent	1221	1146	1105	1081	1045
Bare-metal stent	1211	1115	1066	1037	1000

B Primary Efficacy End Point



No. at Risk	0	90	180	270	390
Drug-coated stent	1221	1167	1130	1098	1053
Bare-metal stent	1211	1131	1072	1034	984

Post Hoc of ZEUS, 2016

MHIF Cardiovascular Grand Rounds | May 3, 2021

↓ Death, MI, TVR, ST

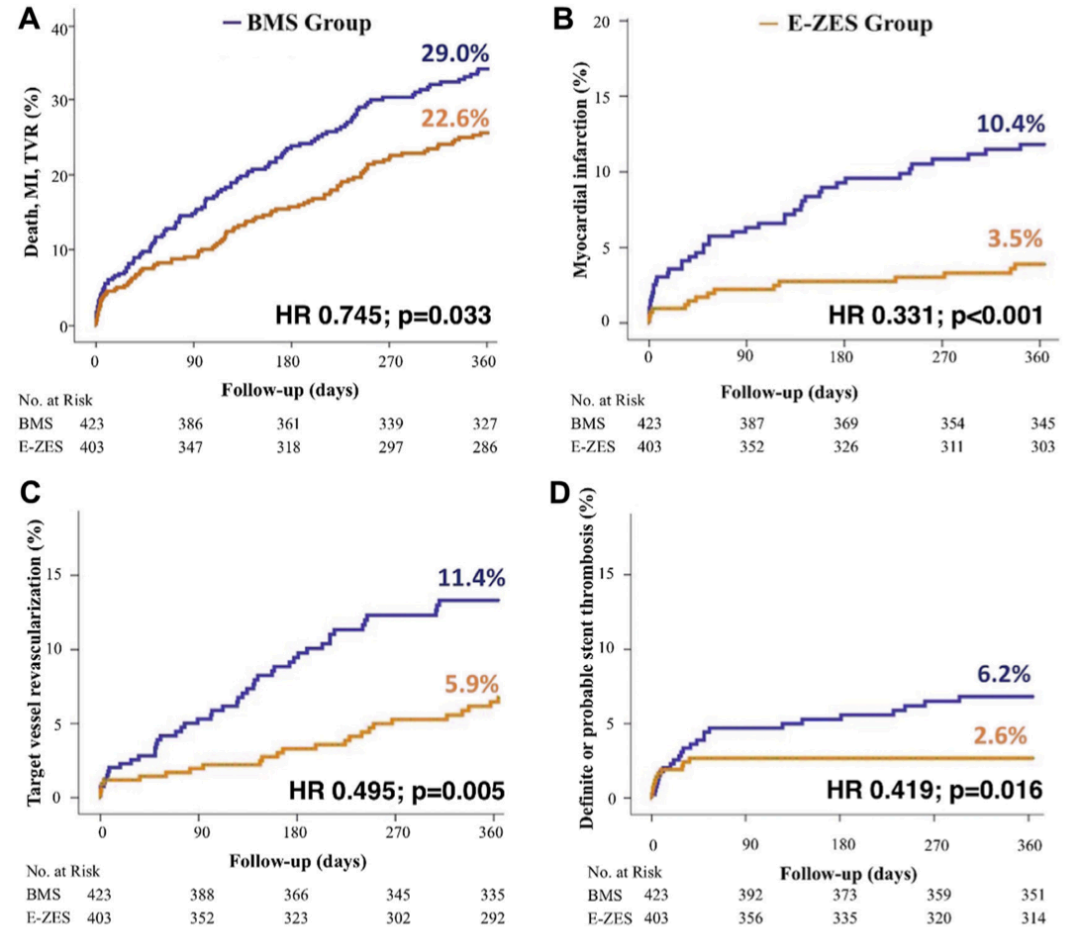
Design: ZES (Endeavor Spirit) vs BMS, 1:1 Randomization, Single Blinded, High Bleeding Risk Patients

Duration: 12 months, 828 patients

Primary Outcome: MACE (Death, MI, TVR)

ACS vs SIDH: 35% SIHD

DAPT Duration: 1 month (ASA, P2Y12i) followed by ASA



Rate of events for primary composite endpoint of death, myocardial infarction (MI), and target vessel revascularization (TVR) (A), MI (B), TVR (C), or definite or probable stent thrombosis (D) at 12 months. BMS = bare-metal stent(s); E-ZES = zotarolimus-eluting Endeavor Sprint stent(s); HBR = high bleeding risk; HR = hazard ratio.

J Am Coll Cardiol Intv 2016;9:426-36

LEADERS FREE II 2018

↓ Lower TLR, Lower Cardiac Death or MI

Design: DCS (Biolimus, BioFreedom Stent) vs BMS (historical cohort from LEADERS FREE 2015), High bleeding risk patients

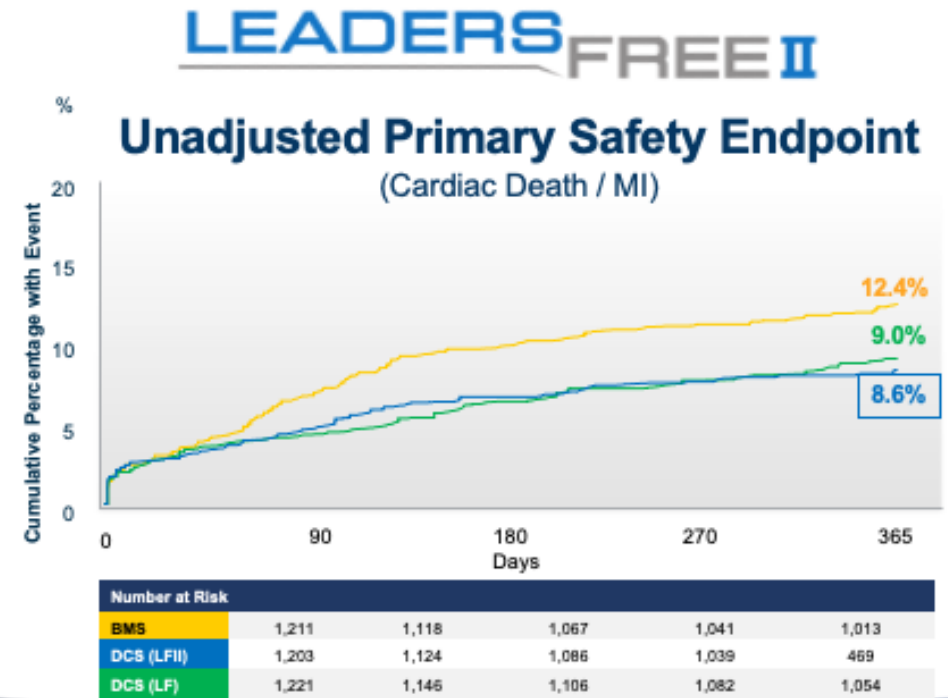
Duration: 12 months, 1,203 patients

Primary Safety Outcome: composite of cardiac death, or MI

Primary Efficacy Outcome: TLR

DAPT Duration: 1 month (ASA, PLAVIX) followed by ASA

SIHD/ACS: 44% ACS



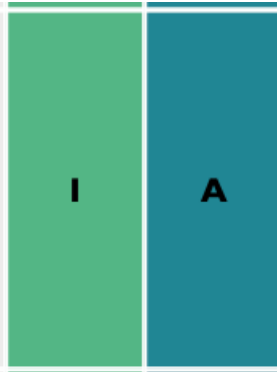
This trial led to the FDA approval of Biolimus A9

~ Similar risk of ST

The End of BMS? LEADERS FREE II Shows Superiority of Polymer-Free, Drug-Coated Stent

DES are recommended over bare-metal stents for any PCI irrespective of:

- Clinical presentation.
- Lesion type.
- Planned non-cardiac surgery.
- Anticipated duration of DAPT.
- Concomitant anticoagulant therapy.^{354,365,366}



BMS < DES (New Gen)

European Heart Journal (2021) 42, 1289–1367

ONYX ONE 2020

Design: Polymer based ZES (Resolute) vs Polymer-free DCS (Biolimus, Biofreedom), Randomized, High Bleeding Risk Patients

Duration: 1 year, 1996 patients

Primary Outcome: Cardiac Death, MI or ST

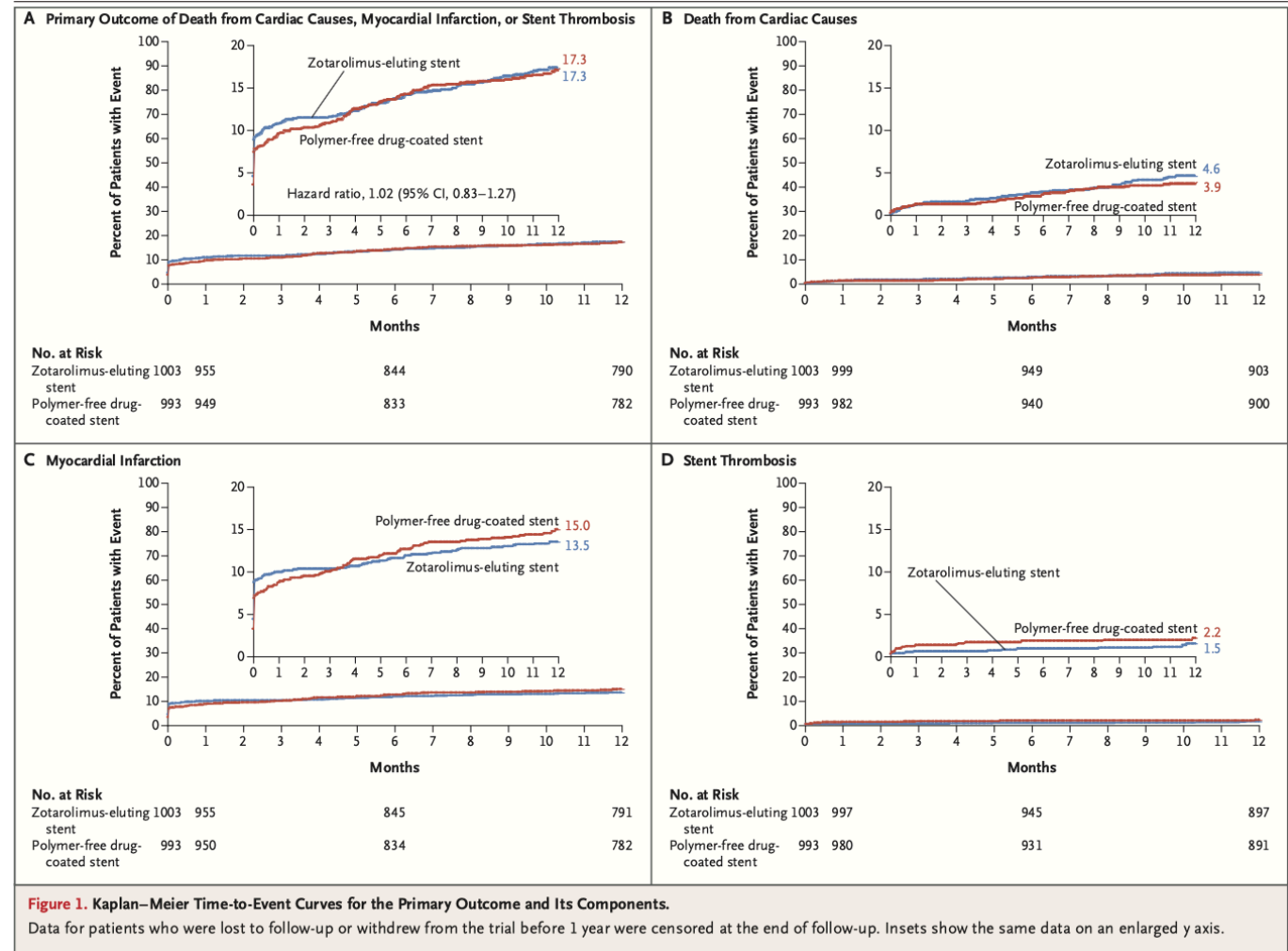
Efficacy Outcome: composite Cardiac Death, Target Vessel MI, TLR

Limitations: High Ischemic and Bleeding events (high risk population studied?)

ACS vs SIDH: 38% SIHD

DAPT Duration: 1 month (ASA, P2Y12i) followed by ASA

Complex Lesions: 80%



XIENCE 28 and XIENCE 90, presented TCT 2020

MHIF Cardiovascular Grand Rounds | May 3, 2021

Design: HBR patients, Xience (Everolimus) 1m vs 12m DAPT or 3m vs 12m DAPT (Xience 28 and Xience 90 patients compared to historical control)

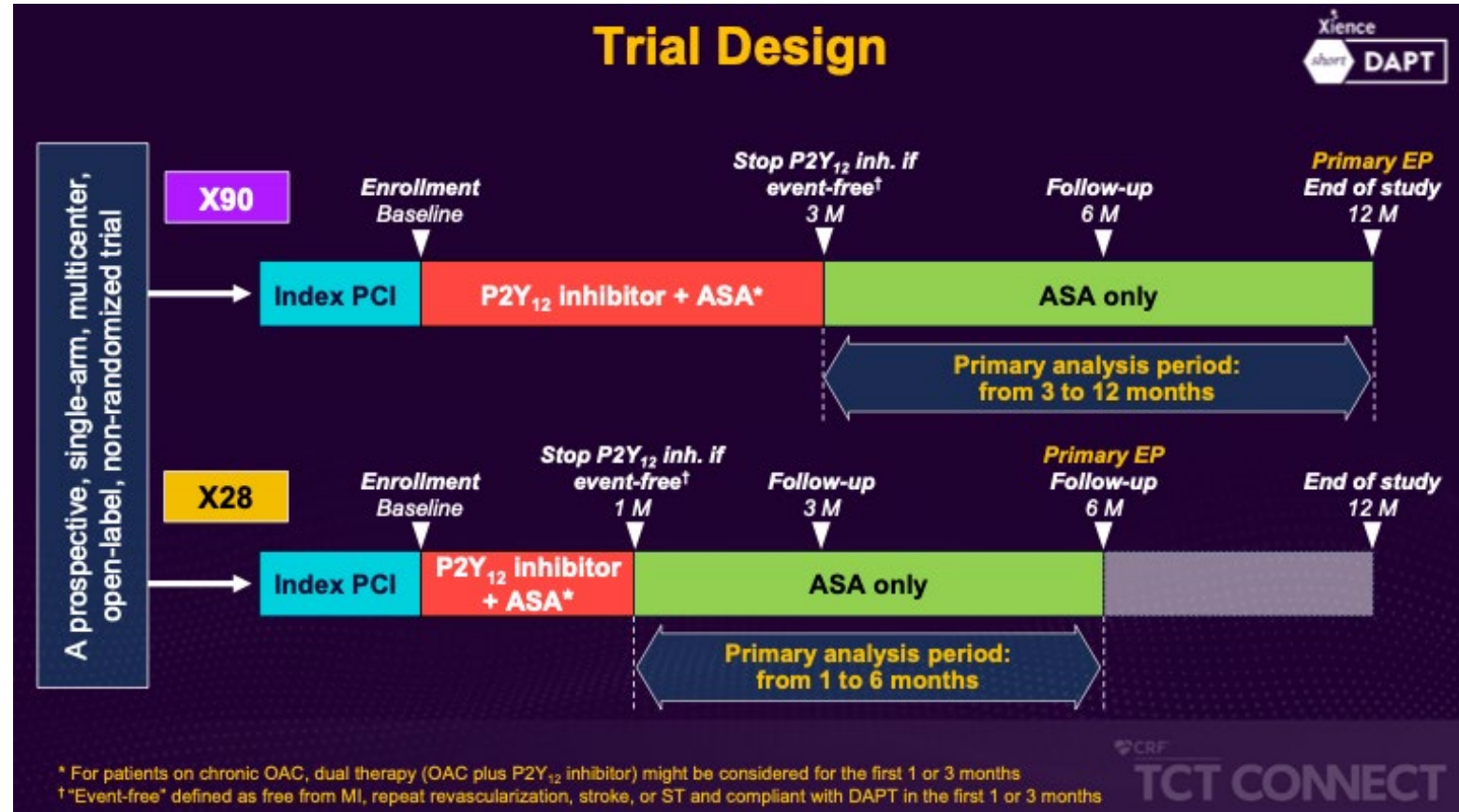
Primary Safety Outcome: all death or MI

Clinically Relevant Bleeding: 1 or 3m vs 12m DAPT

Limitations: excluded STEMI, LM, Grafts, CTO, ISR

ACS vs SIDH: ~35%

Complex Lesions: ~40%



<https://clinicaltrials.gov/ct2/show/NCT03815175>

<https://www.xiencestent.com/us/featured-trials/xience-90-short-dapt-study-xience-safety-difference/?L=0#:~:text=The%20XIENCE%2090%20trial%20is,as%20early%20as%2028%20days.>

ACS Patients

DAPT STEMI 2018

Primary Outcomes favored SAPT

Design: RCT, STEMI only, (Resolute Onyx, Zotarolimus eluting) 1:1, 6m (followed by ASA) vs 12m DAPT

Duration: 24 months months, 870 patients

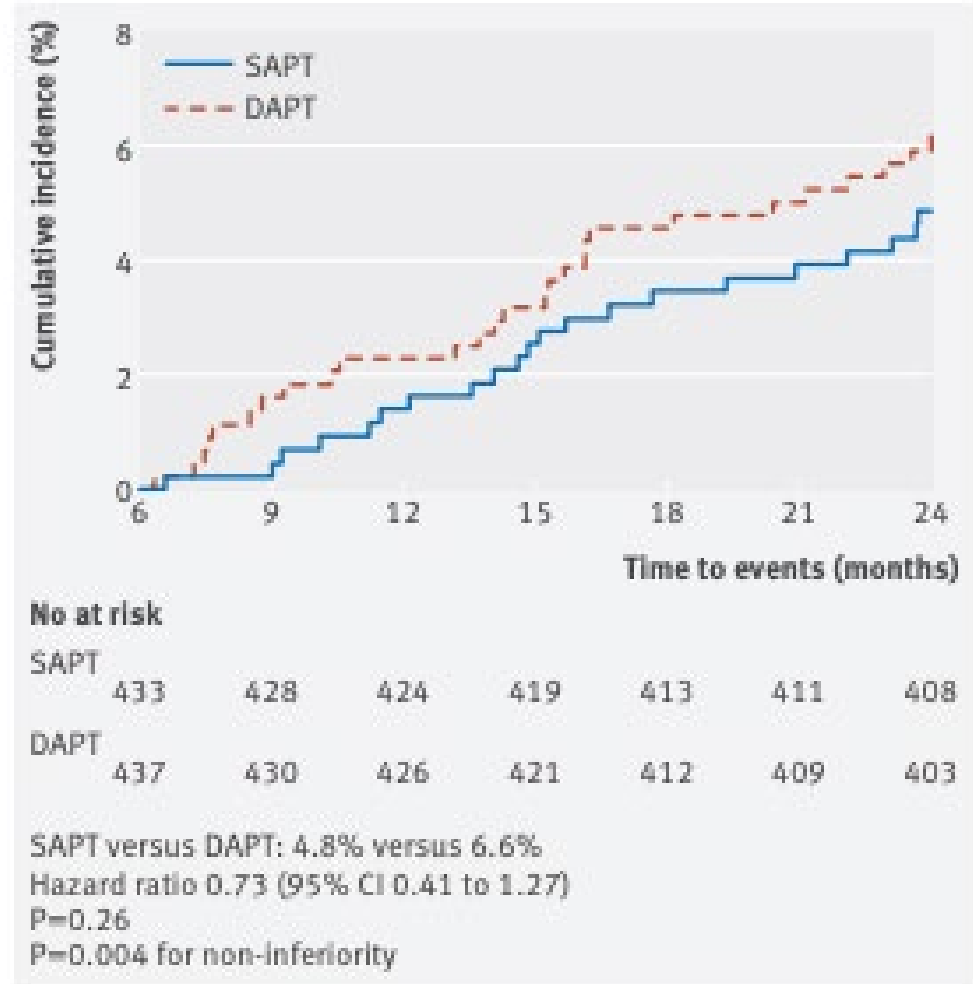
Primary Safety Outcome: all-cause mortality, MI, CVA, Any Revascularization, Major Bleeding

Limitations: low sample size, high drop out after 6 months

P2Y12i: Plavix 40% Ticagrelor 30% Prasugrel 30%

Complex: 25%, excluded LM

BMJ 2018;363:k3793 | doi: 10.1136/bmj.k3793



SMART DATE 2018

More MACE and MI with 6m vs 12m

Design: RCT, ACS only, 6m vs 12m DAPT followed by ASA (Xience (Everolimus), Resolute Onyx (Zotarolimus), Biomatrix (Biolimus))

31 sites, South Korea

Duration: 18 months, 2,712 patients

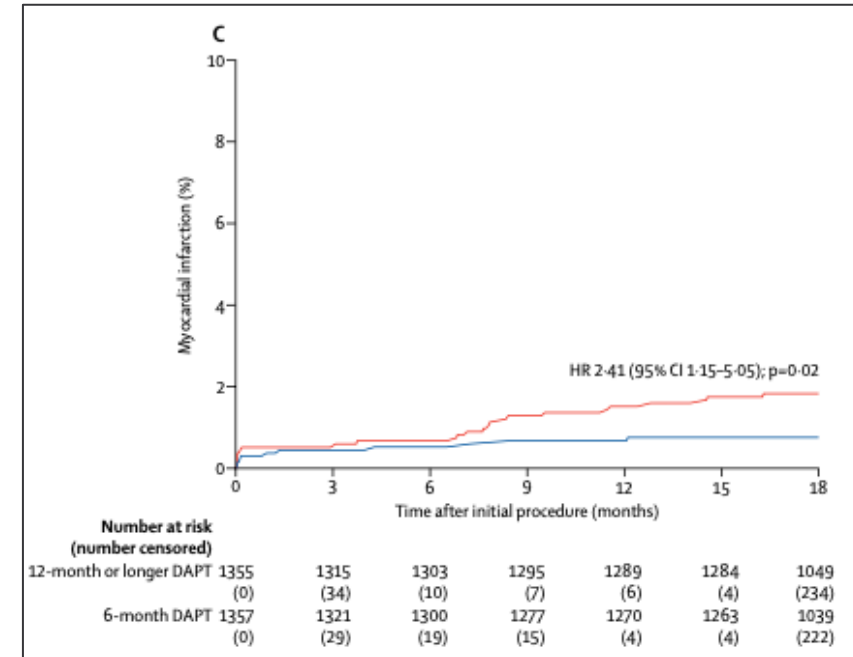
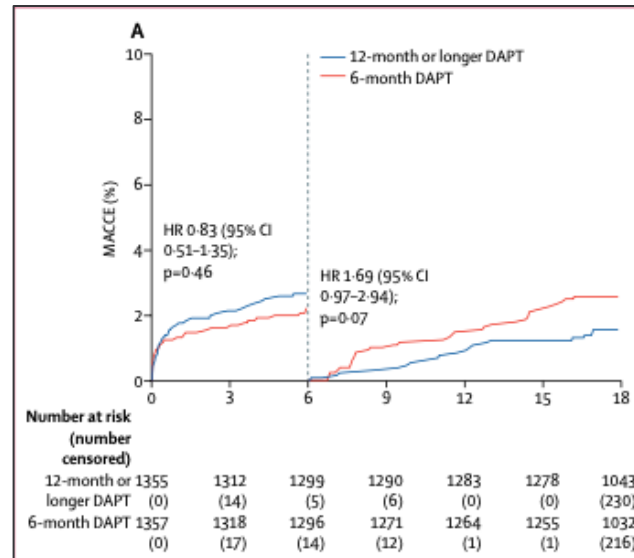
Primary Safety Outcome: MACCE – the composite of all-cause death, MI or stroke

Secondary Endpoint: BARC 2-5 bleeding

P2Y12i: Plavix 82%

Limitations: High rates of Plavix use (even though Ticagrelor and Prasugrel are superior)

Complex: 45%



Lancet 2018; 391: 1274-84

BMS Obsolete

**“Simple Coronary Lesion/SIHD” in HBR 1-3
month DAPT (6 month per guidelines)**

**“Complex Lesions/ACS” in HBR 3-6 months
DAPT (12 month per guidelines)**

Short DAPT followed by P2Y12i

TWILIGHT 2019

Design: RCT, 1:1 double blind, ASA+Ticagrelor 3m followed by Ticagrelor monotherapy VS ASA+Ticagrelor for 12 months

Duration: 12 months, 7,119 patients (HBR and High Ischemic Risk)

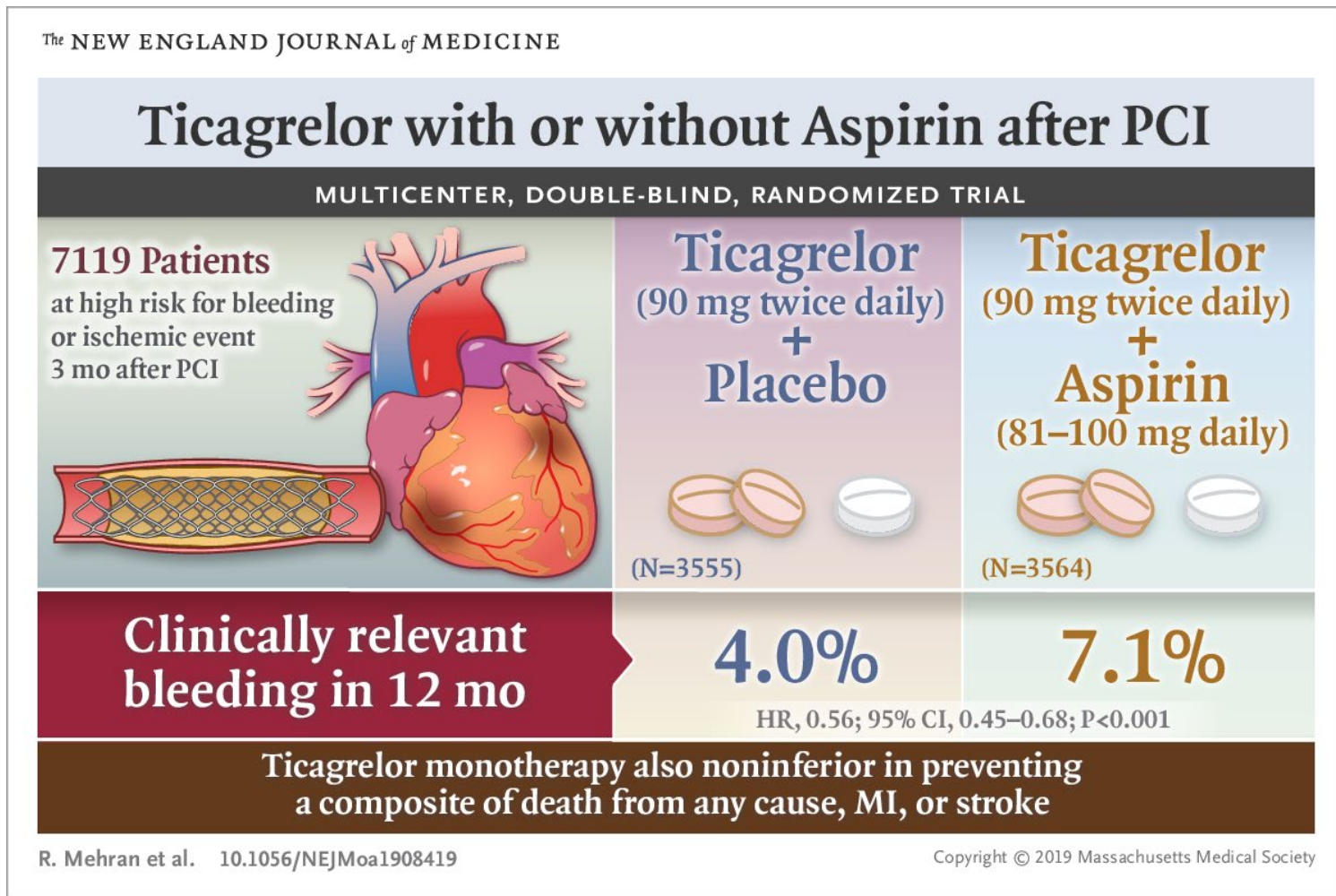
Primary Outcome: BARC 2,3, or 5 bleeding

Limitations: excluded STEMI, shock

ACS vs SIDH: ACS 64%

DAPT Duration: 3 vs 12 months

Lesion Types: Complex



Mehran R, Baber U, Sharma SK, et al. Ticagrelor With or Without Aspirin in High-Risk Patients After PCI. *N Engl J Med* 2019;381:2032-42.

STOPDAPT-2 2019

Design: RCT, 1 month DAPT followed by Clopidogrel monotherapy vs 12 month DAPT followed by ASA monotherapy (DES- Xience, Everolimus eluting)

Duration: 1 year, 3,045 patients

Primary Outcome: Death, myocardial infarction (MI), stent thrombosis, stroke, TIMI major/minor bleeding

Secondary Outcome: TIMI bleeding

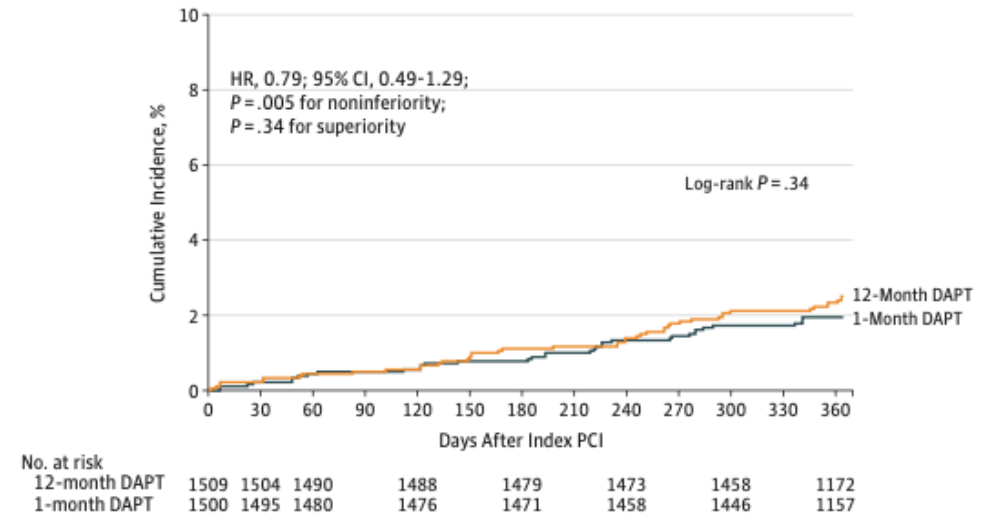
ACS vs SIDH: 62% SIHD

DAPT Duration: 1 month vs 12 months

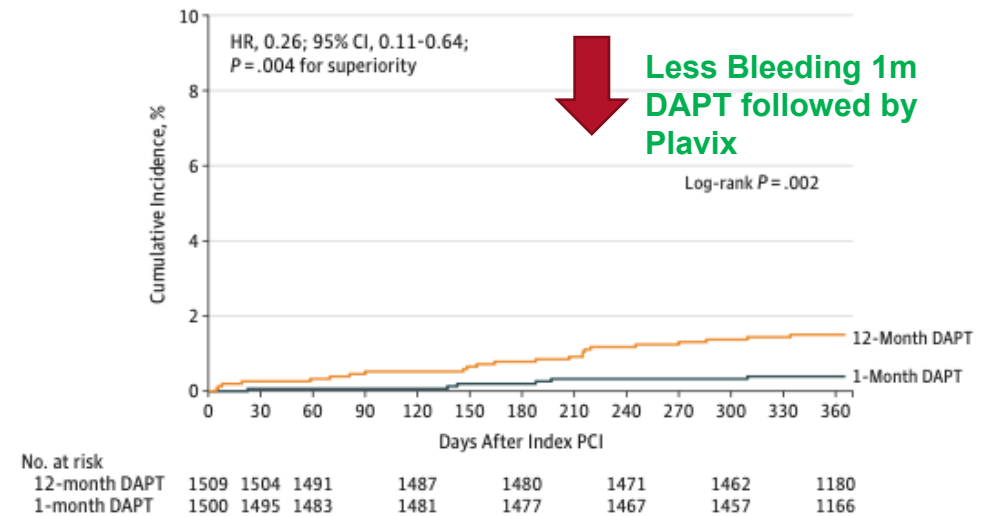
Lesion Types: ~30% complex

Watanabe H, Domei T, Morimoto T, et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. *JAMA* 2019;321:2414-27.

B Composite of cardiovascular death, MI, definite stent thrombosis, or ischemic and hemorrhagic stroke



C TIMI major/minor bleeding



Design: RCT, (Orsiro, Ultrathin Sirolimus eluting), ASA+Ticagrelor 3m followed by Ticagrelor monotherapy VS ASA+Ticagrelor for 12 months in ACS patients

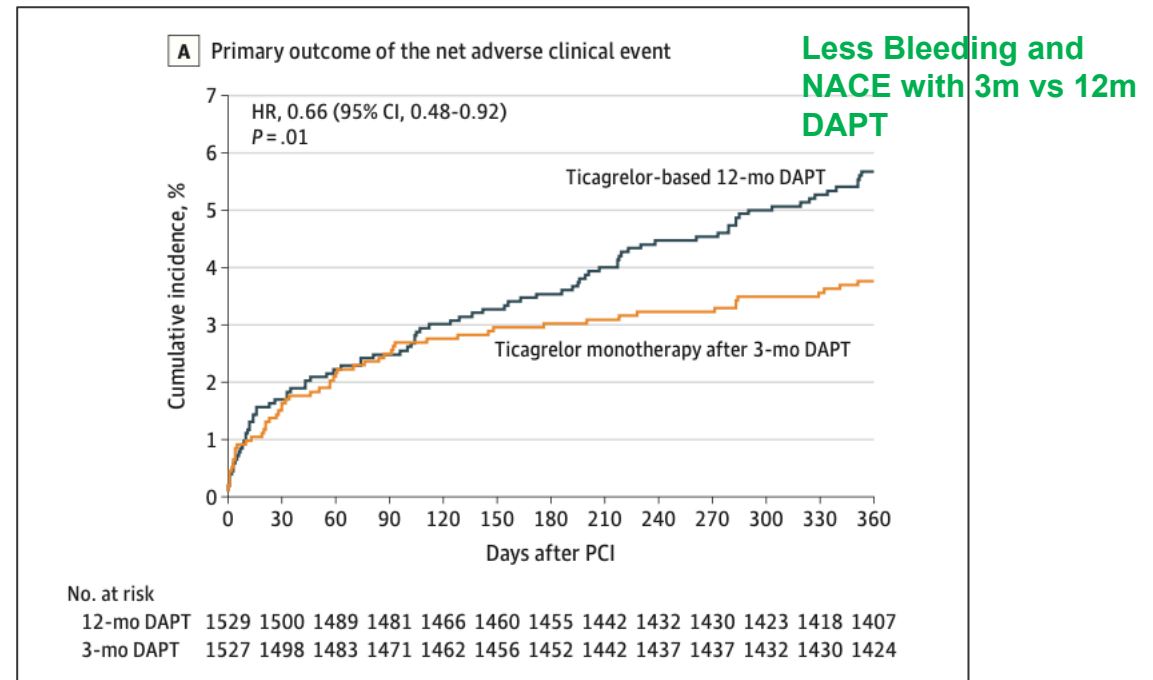
Duration: 12 months, 3,056 patients


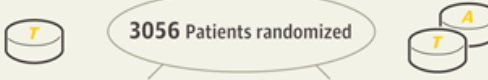

Primary Outcome: Composite of death, MI, ST, TVR or TIMI major bleeding (NACE)

ACS: 1/3rd STEMI

Lesion Types: Complex 15%

Limitations: South Korea– High rates of IC imaging used, **excluded HBR patients**



<p>POPULATION</p> <p>2428 Men 628 Women</p>  <p>Adults with acute coronary syndrome treated with drug-eluting stents</p> <p>Mean age: 61 years</p>	<p>INTERVENTION</p> <p>3056 Patients randomized</p> <p>1527 Ticagrelor monotherapy after 3 months of DAPT 100 mg aspirin once daily and 90 mg ticagrelor twice daily for 3 months, then 90 mg ticagrelor twice daily for 9 months</p> <p>1529 Ticagrelor-based DAPT for 12 months 100 mg aspirin once daily and 90 mg ticagrelor twice daily maintained for 12 months</p> 	<p>FINDINGS</p> <p>Net adverse clinical events at 12 months</p> <p>Ticagrelor monotherapy after 3 months of DAPT 3.9% (59 of 1527 patients)</p> <p>Ticagrelor-based DAPT for 12 months 5.9% (89 of 1529 patients)</p> <p>The difference was significant: absolute difference, -1.98% (95% CI, -3.50 to -0.45)</p>
<p>LOCATIONS</p> <p>38 Centers in South Korea</p> 	<p>PRIMARY OUTCOME</p> <p>1-year net adverse clinical events, defined as a composite of major bleeding and adverse cardiac and cerebrovascular events (death, myocardial infarction, stent thrombosis, stroke, or target-vessel revascularization)</p>	<p>© AMA</p>

Kim B-K, Hong S-J, Cho Y-H, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. Published June 16, 2020. doi:10.1001/jama.2020.7580

Complex Anatomy/ACS : Ticagrelor>Plavix

Short DAPT (3m) followed by P2Y12i (HBR)

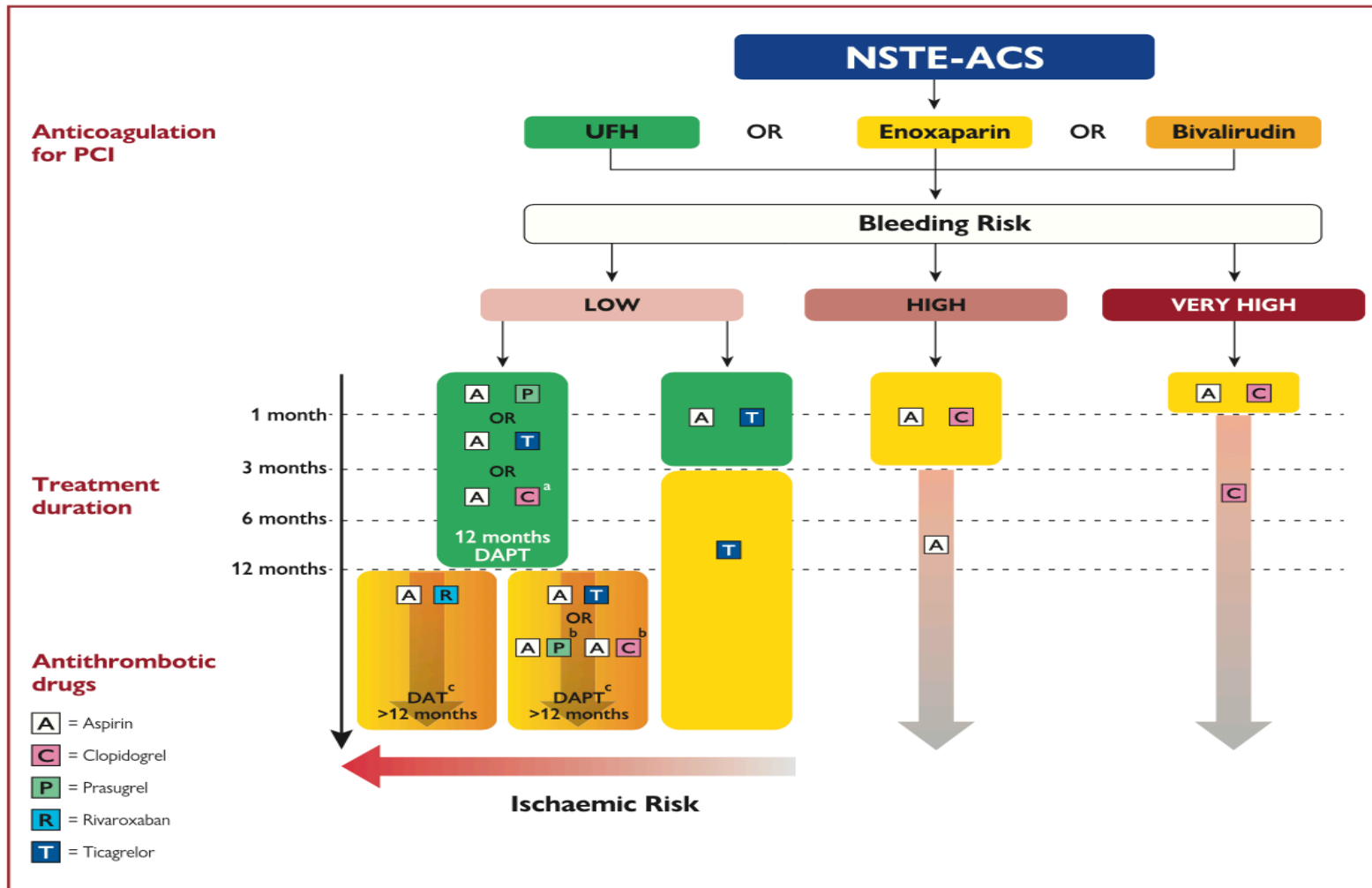
BMI: High BMI reduce P2Y12i intensity (studies out of South East Asia VS USA)

East Asian: CYP2C19 mutation, poor Clopidogrel metabolism

Studies out of Japan/Korea: IVUS/OCT use

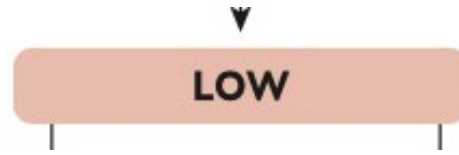
Time for New Guidelines incorporating Short DAPT?

ESC 2020 GUIDELINES ON DAPT (ACS)

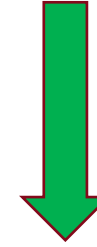


©ESC 2020

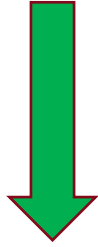
ESC 2020 GUIDELINES ON DAPT (SIHD)



**6 month DAPT
(irrespective of
stent type)**



**3 month DAPT
(irrespective of
stent type)**

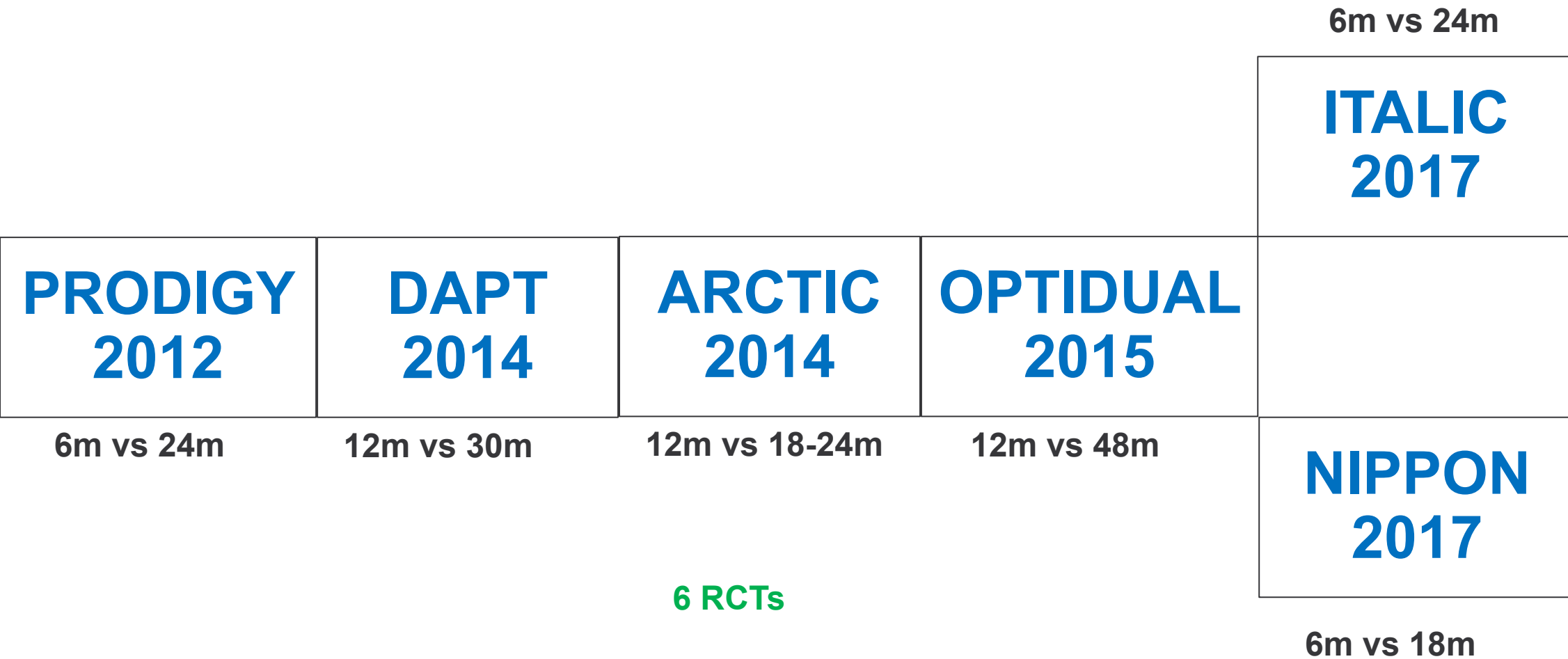


**1 month DAPT
(irrespective of
stent type)**

Scenario 4:

My patient had PCI in 2003 with a 1st Gen DES. I am hesitant to go from DAPT to SAPT.

AHA/ACC 2016 Guidelines: SIHD>6m and ACS>12m (Class 2b) if tolerating well and at low bleeding risk



Plavix 100%
1st Gen DES or
BMS 50%



Plavix 65%
1st Gen DES 40%



Plavix 90%
1st Gen DES 40%



Plavix 100%
1st Gen DES 35%



Plavix 99%
2nd Gen DES 100%

6m vs 24m



**ITALIC
2017**

**PRODIGY
2012**

**DAPT
2014**

**ARCTIC
2014**

**OPTIDUAL
2015**

6m vs 24m

12m vs 30m

12m vs 18-24m

12m vs 48m

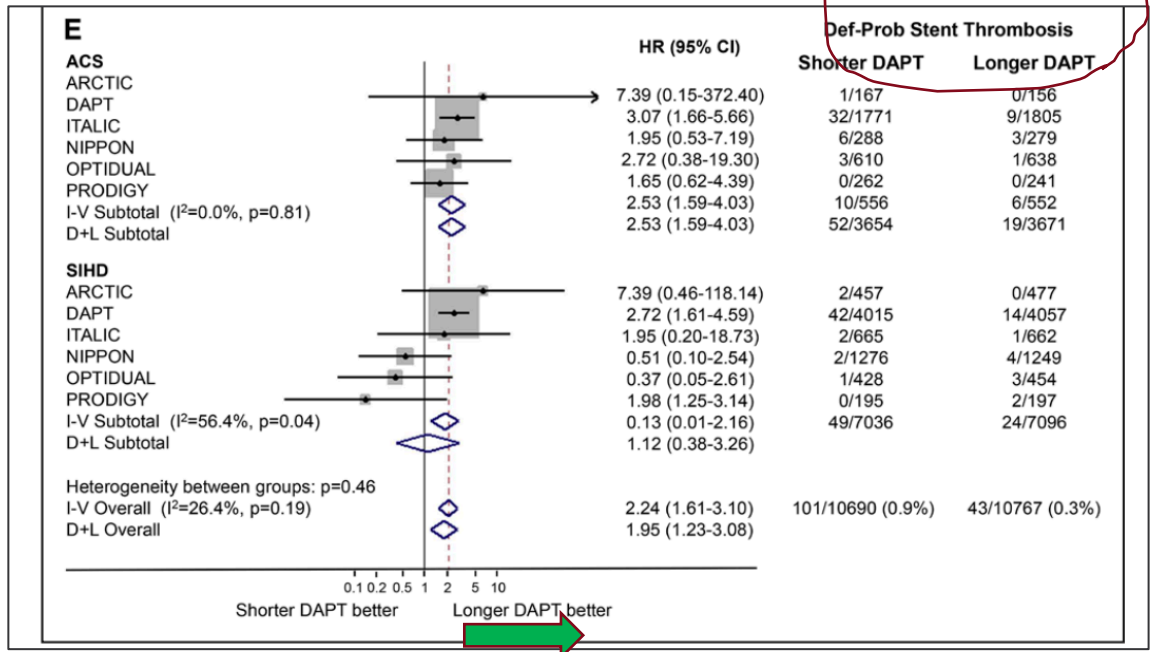
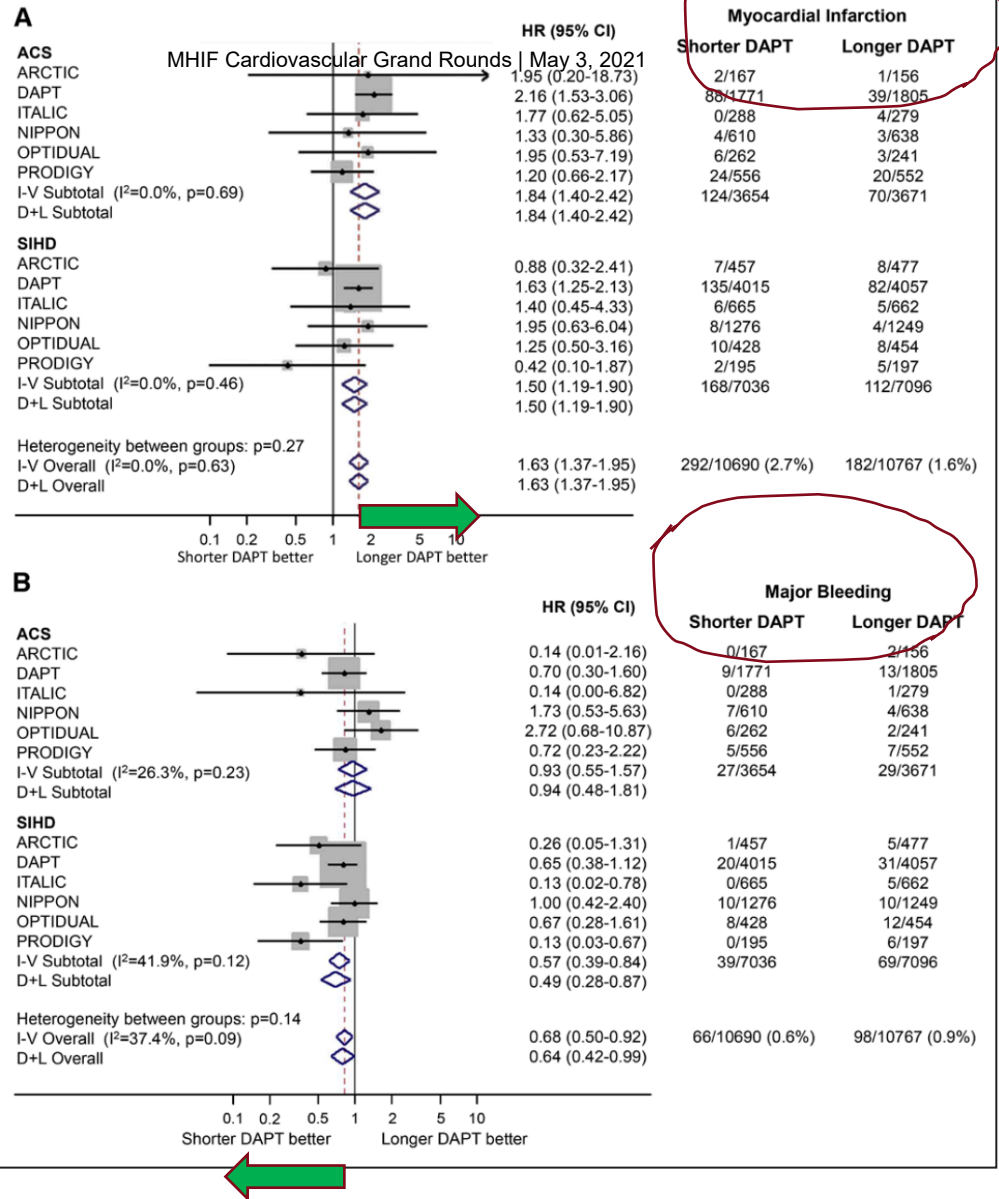
**NIPPON
2017**

6m vs 18m

Plavix 99%
2nd Gen DES 100%



Meta-Analysis 2019 (<12m vs >12m DAPT after PCI)

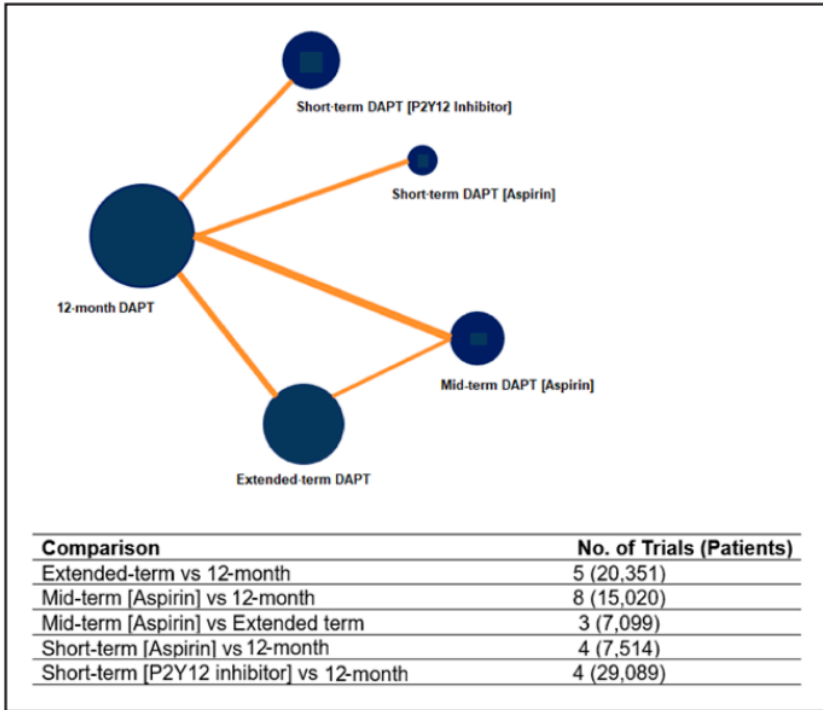


Benefit of >12m DAPT more apparent for ACS not SIHD patients

Circ Cardiovasc Interv. 2019;12:e007541. DOI: 10.1161/CIRCINTERVENTIONS.118.007541



Network Meta-analysis, 2020 (79,073 patients)



<3m (P2y12i mono) vs 12m

>12m vs All

MI

~



Bleeding



Figure 1. Network of DAPT interventions.

The area of the circles is based on the total number of patients for each treatment among all trials. The thickness of the lines is based on the total number of studies comparing the 2 treatments. DAPT indicates dual antiplatelet therapy.

Circulation. 2020;142:1425–1436. DOI: 10.1161/CIRCULATIONAHA.120.046308

Shared Decision Making

- DAPT Score (≥ 2 favors $>12m$ DAPT)
- PRECISE DAPT Score (<25 favors prolonged DAPT)
- PCI Complexity
- Stent Type
- Bleeding Risk

Evolving Concepts

- **Genotyping** (Clopidogrel non-responders) **and Platelet Function testing** to escalate or de-escalate therapy
- **Low dose Rivaroxaban** (with 2.5mg BID + ASA: COMPASS) or (ASA+PLAVIX: ATLAS ACS 2 TIMI-51), **underutilized** (**↓** MACE, **↑** BLEEDING)

ONGOING TRIALS

- MASTER DAPT (1 vs 6m DAPT in HBR) *Ultimaster Tansei stent* (NCT03023020)
- BIOFLOW DAPT (1m DAPT) *Orsiro stent* (NCT04137510)
- TARGET-SAFE (1 vs 6m DAPT in HBR) *Firehawk™ Stent* (NCT03287167)

Thank You

Dr Burke

Dr Brilakis

Dr Chavez

Dr Garcia

Dr Goessl

Dr Mooney

Dr Poulose

Dr Sorajja

Dr Traverse

Dr Wang