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Clinical Meeting & Exhibition

(313-L01) Rolling the Dice with Triple Therapy

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Disclosure

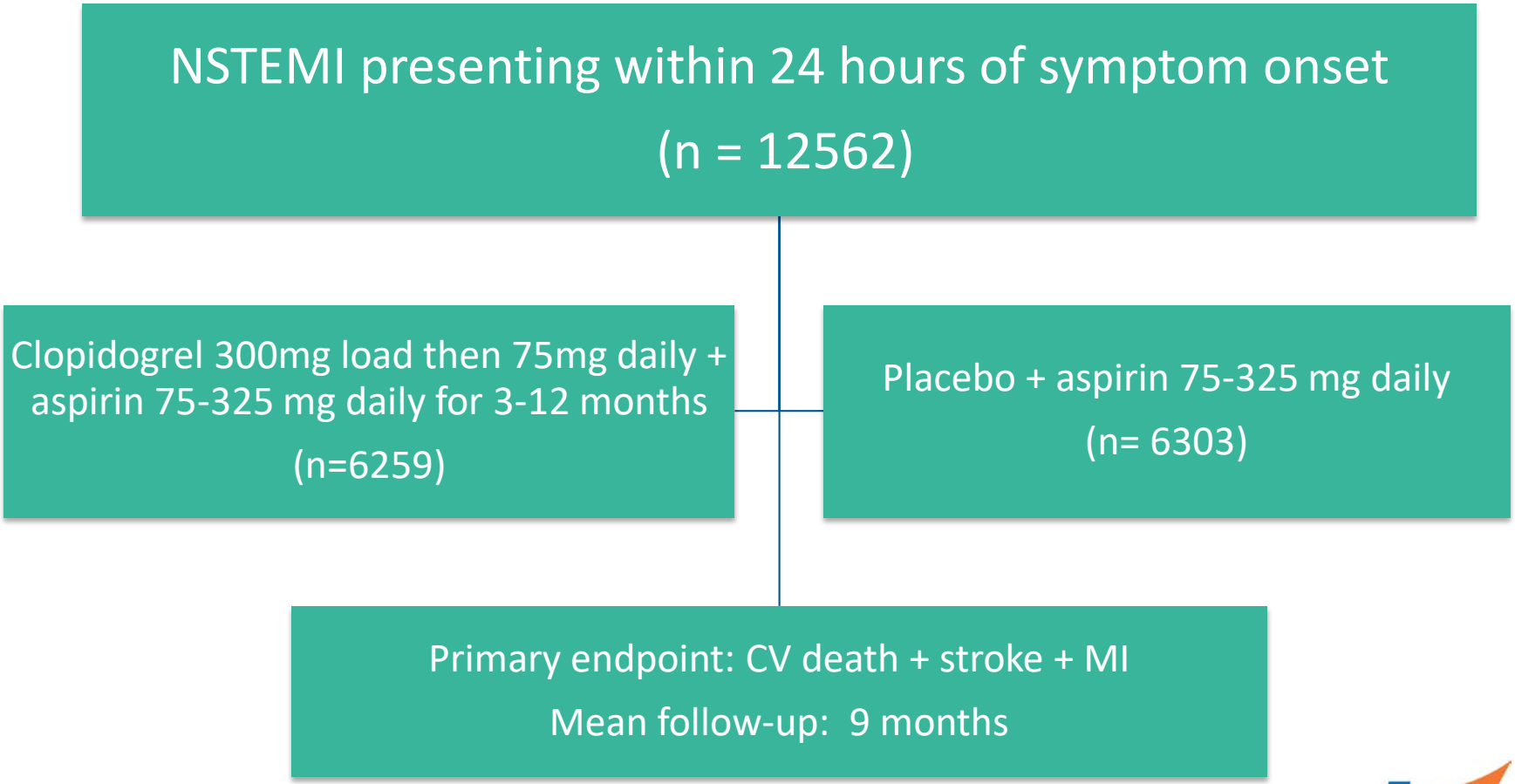
- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.

Antithrombotic therapy for ACS

- Aspirin
- Clopidogrel
- Prasugrel
- Ticagrelor
- Vorapaxar
- Cilostazol
- Combination therapy – Dual Antiplatelet Therapy (DAPT)
- Oral Anticoagulation (OAC)
  - "Triple Therapy"
    - DAPT + OAC
    - Triple antiplatelet therapy

DAPT: How did it get here?

CURE study



Yusuf S, et al. *Eur Heart J.* 2000;21:2033-41
The CURE Trial Investigators. N Engl J Med. 2001;345:494-502

CURE: Efficacy results

Outcome	Clopidogrel	Placebo	RRR	p value
CV death/MI/Stroke (primary endpoint)	9.3%	11.8%	20%	< 0.001
MI	5.2%	6.7%	23%	< 0.001
Stroke	1.2%	1.4%	14%	NS
CV Death	5.1%	5.5%	7%	NS

Number needed to treat to prevent one primary endpoint event = 40 patients for 9 months

The CURE Trial Investigators. N Engl J Med. 2001;345:494-502.

CURE: Safety results

Endpoint	Clopidogrel	Placebo	p value
Major bleeding	3.7%	2.7%	0.001
Life-threatening bleeding	2.2%	1.8%	NS
Non life-threatening bleeding	1.5%	0.9%	0.002
Minor bleeding	5.1%	2.4%	<0.001
Transfusion of ≥ 2 units blood	2.8%	2.2%	0.02
Total bleeding complications	8.5%	5%	<0.001

Number needed to harm = 100

Major bleeding episodes were defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood.

Minor bleeding: other hemorrhages that led to interruption of study medication

The CURE Trial Investigators. N Engl J Med. 2001;345:494-502.

CURE: Life-threatening bleeding

	Clopidogrel	Placebo
Life-threatening	2.2%	1.8%
Fatal bleeding	0.2%	0.2%
Hemoglobin drop > 5 g/dL	0.9%	0.9%
Hypotension requiring inotropes	0.5%	0.5%
Hemorrhagic stroke	0.1%	0.1%
Surgery required	0.7%	0.7%
Received > 4 units of blood	1.2%	1.0%

The CURE Trial Investigators. N Engl J Med. 2001;345:494-502.

CURE: Conclusions

- Clopidogrel use associated with a 20% RRR in the primary endpoint:
  - Driven by reduction in MI
- Major bleeding increased by 38%
  - No difference in life-threatening bleeding
  - Minor and total bleeding were significantly increased

The CURE Trial Investigators. N Engl J Med. 2001;345:494-502.

Complications of Stents

- Stent thrombosis
  - This is a complication of ALL stents
  - Is the most feared complication
  - Is the timing of thrombosis different?
- What are the concerns with stent thrombosis?
- Can the risk be modified or minimized?

Kirtane AJ et al. *Circulation* 2011;124:1283-87.

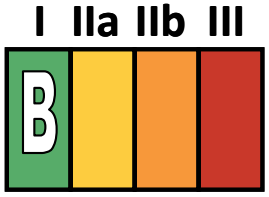
Stent Thrombosis: Why are we concerned?

- Present as MI
  - Usually STEMI

- Always requires emergent PCI for management
- 30-day mortality: 10 – 25 %
- Recurrence: 20% will have a second episode within 2 years

Kirtane AJ et al. *Circulation* 2011;124:1283-87.

Duration of DAPT per STEMI Guideline



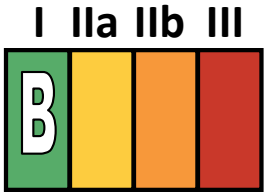
$P2Y_{12}$ inhibitor therapy should be **given for 1 year** to patients with STEMI treated with coronary stents during primary PCI using the following maintenance doses:

- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day

Continuation of a $P2Y_{12}$ inhibitor **beyond 1 year** may be considered in patients undergoing DES placement.

O'Gara PT et al. *J Am Coll Cardiol*. 2013;61:e78-140.

Duration of DAPT per NSTEMI Guideline



$P2Y_{12}$ inhibitor therapy should be **given for at least 1 year** to post PCI patients treated with coronary stents using the following maintenance doses:

- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day

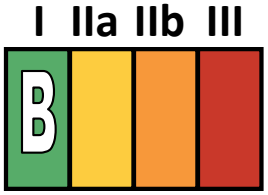
$P2Y_{12}$ inhibitor therapy should be **given for up to 1 year** in patients who do not receive coronary stents using the maintenance doses:

- Clopidogrel 75 mg daily; or
- Ticagrelor 90 mg twice a day

Continuation of a $P2Y_{12}$ inhibitor **beyond 1 year** may be considered in patients undergoing stent implantation

Amsterdam E, et al. *J Am Coll Cardiol.* 2014;64:e139-228

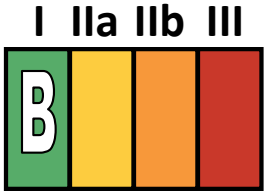
Duration of DAPT per PCI Guideline



$P2Y_{12}$ inhibitor therapy should be **given for at least 1 year** to post PCI patients treated with coronary stents for ACS, using the following maintenance doses:

- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day

Continuation of DAPT beyond 12 months may be considered in patients undergoing DES placement



Clopidogrel should given to patients receiving drug-eluting stents for a non-ACS indication for at least 12 months if the patients are not at high risk of bleeding; or in patients receiving bare metal stents for a non-ACS indication for a minimum of 1 month, but ideally for 12 months

- If the patient received a bare metal stent and is at increased risk of bleeding then clopidogrel should be given for a minimum of 2 weeks

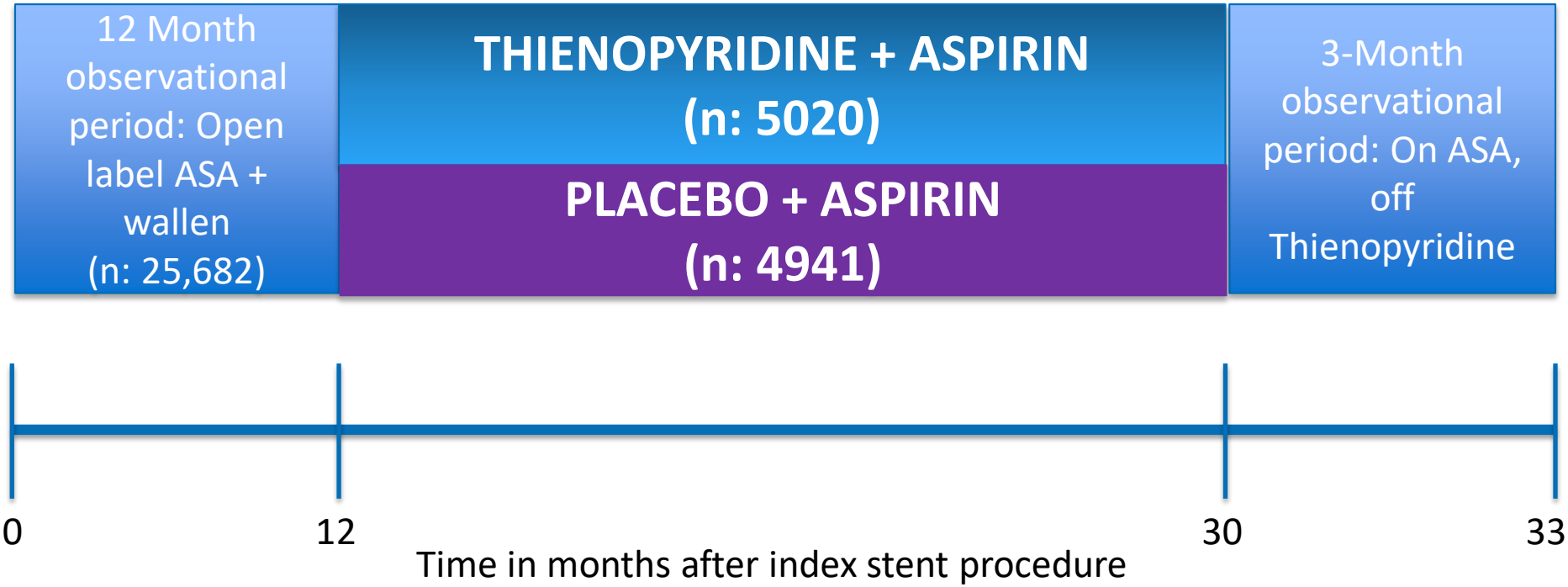
Levine G, et al. *J Am Coll Cardiol.* 2011;58:e44-122

Dual antiplatelet therapy (DAPT) Study

- Objectives:
  - In patients with DES: whether DAPT beyond 12 months is associated with:
    - reduction in stent thrombosis and/or
    - major adverse cardiovascular and cerebrovascular events (MACCE)
      - Defined as a composite of: Death, MI, stroke
  - To determine the impact of prolonged DAPT on moderate or severe bleeding

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

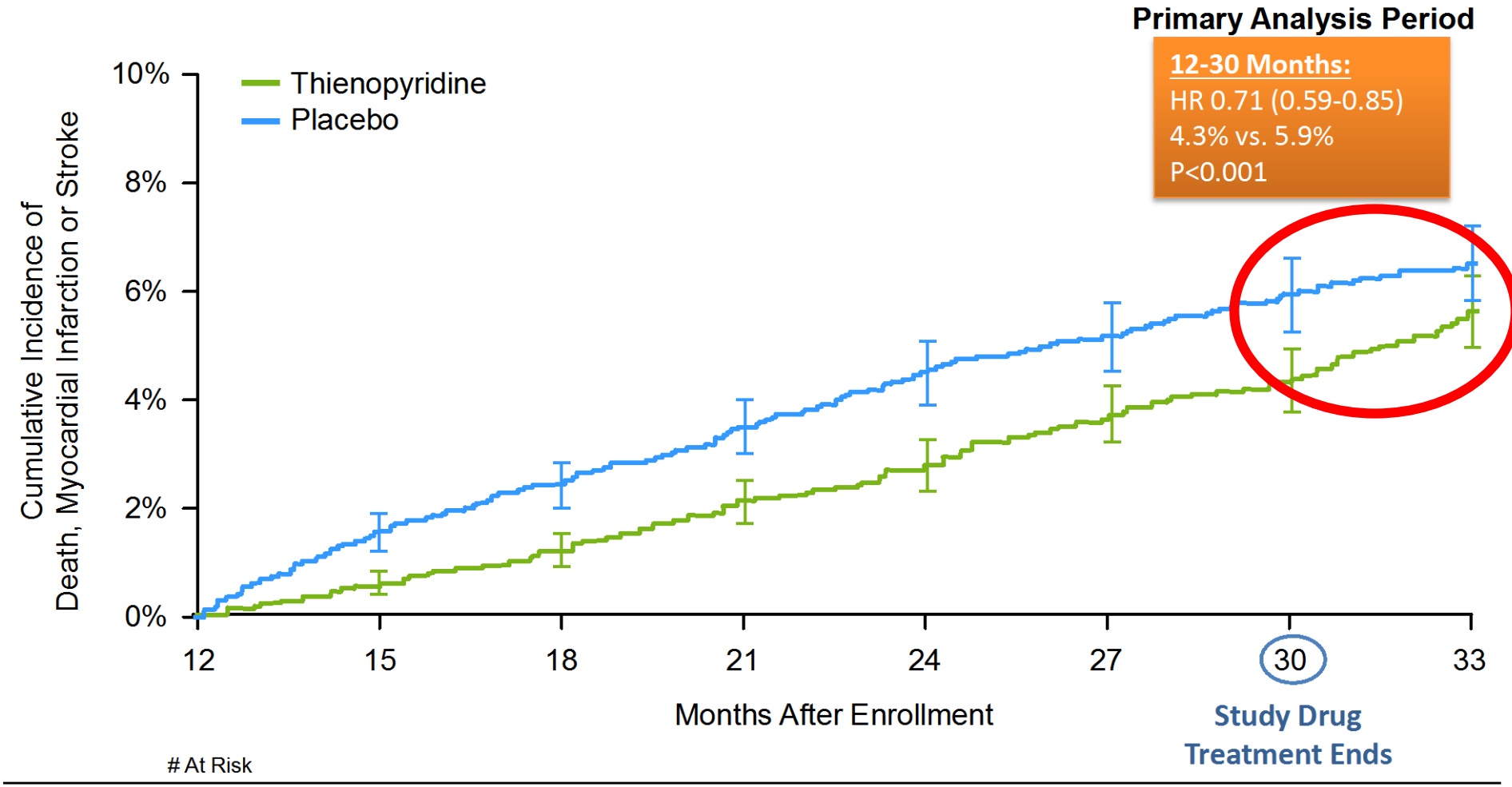
DAPT Study Design



Thienopyridine: Clopidogrel (65%), Prasugrel (35%) of patients enrolled

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

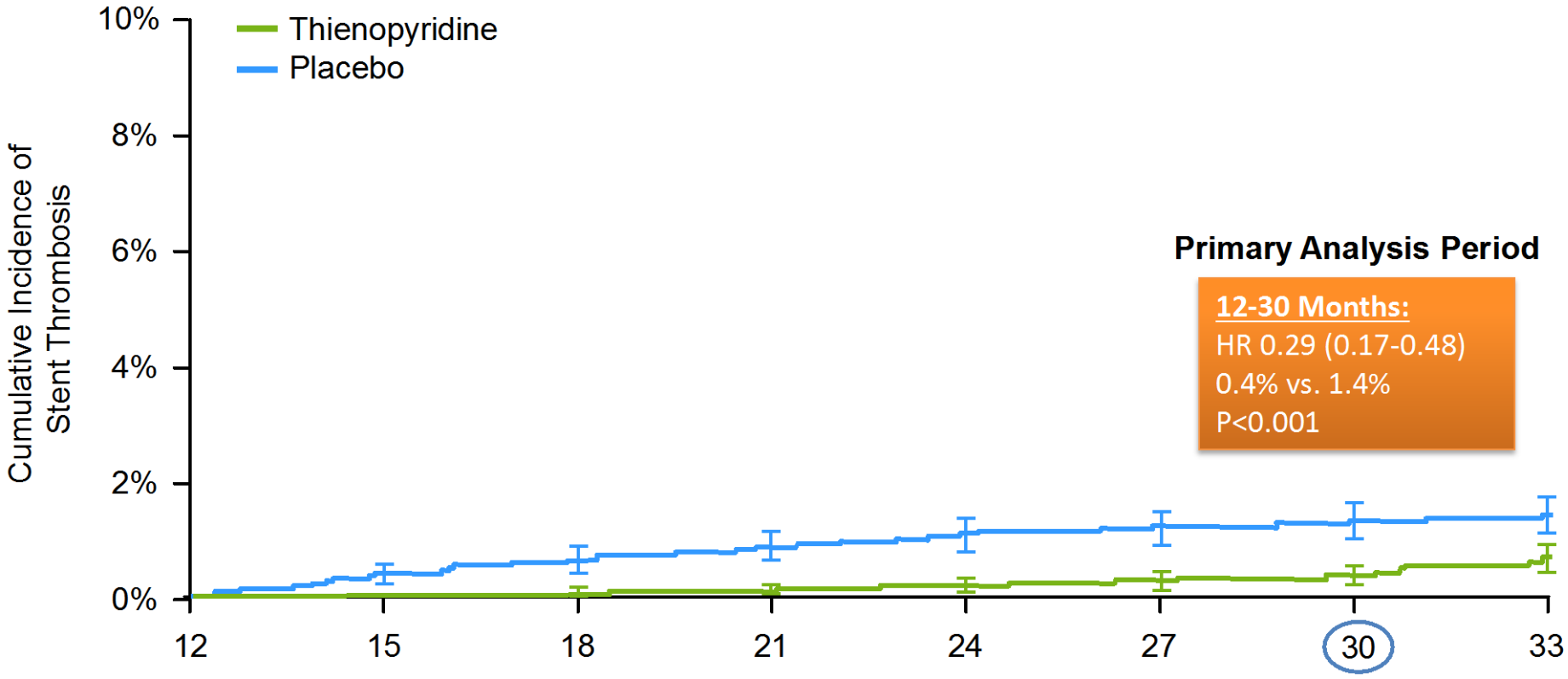
Results: MACCE Endpoint



# At Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

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

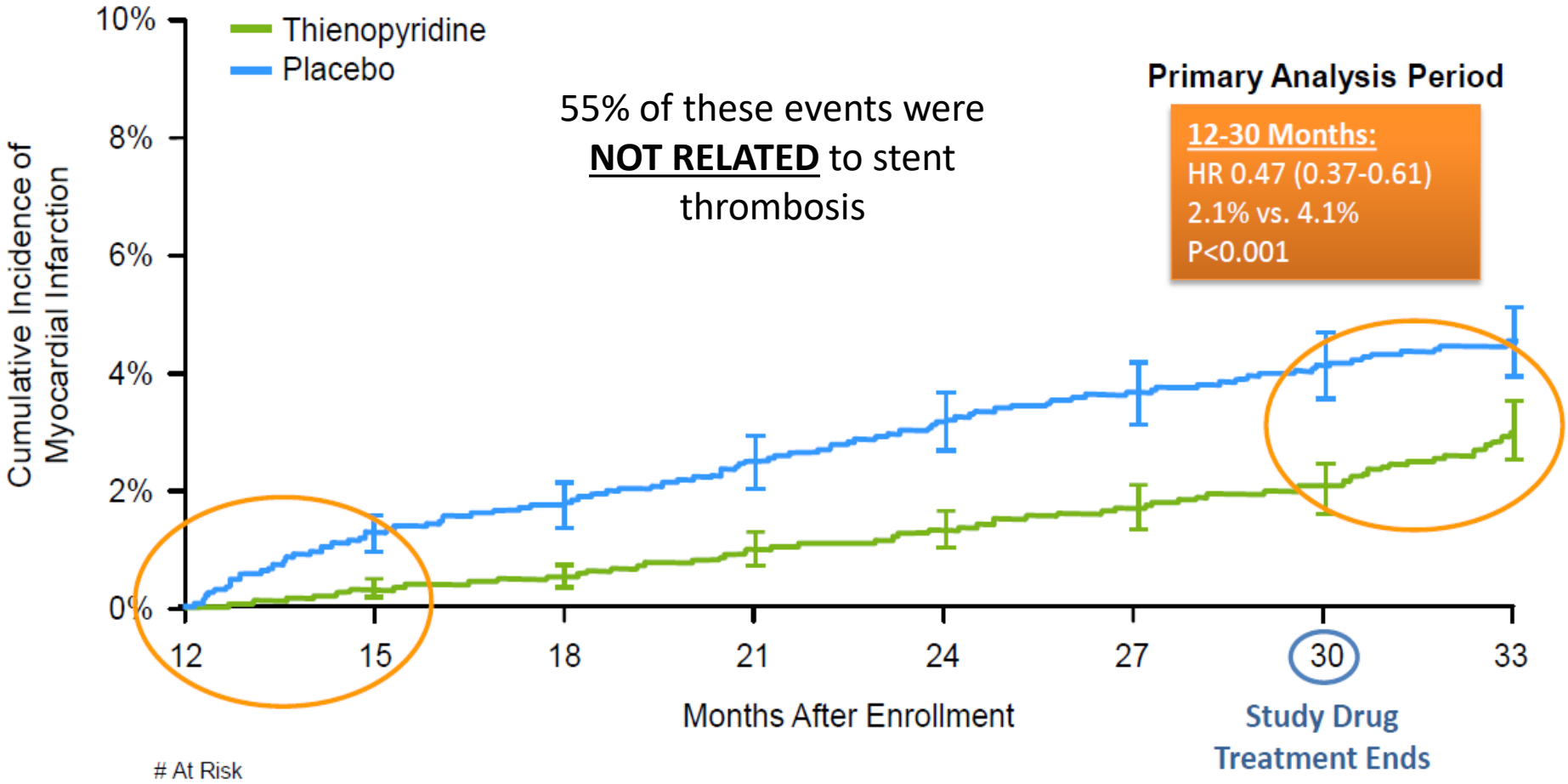
Results: Stent Thrombosis



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

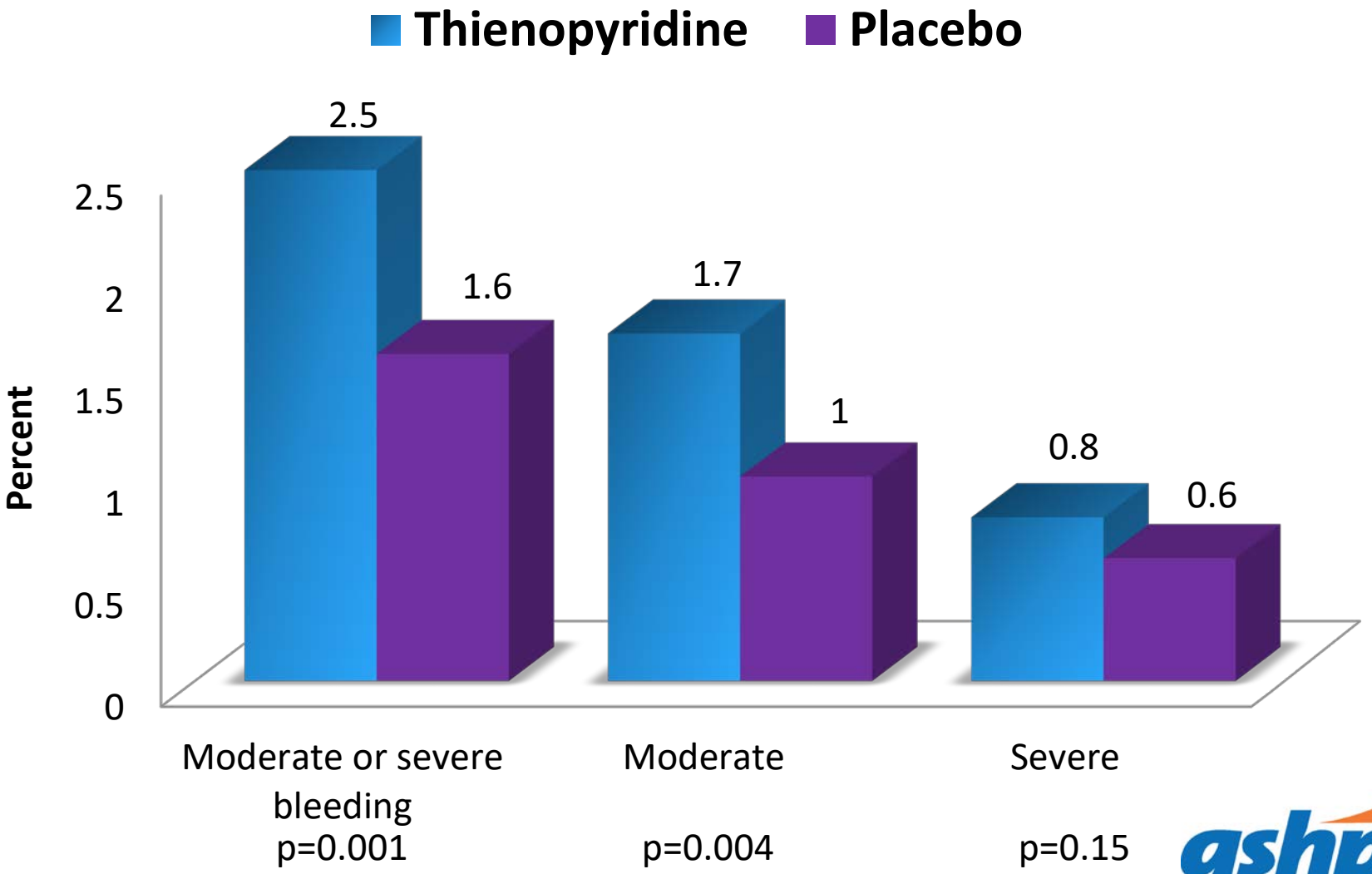
Mauri L et al. N Engl J Med 2014;371:2155-66.

Results: Myocardial Infarction



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

DAPT: Safety results



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DAPT Score: New risk tool to help?

- Objective:
  - To develop a decision tool to identify whether a patient is more or less likely to benefit from prolonged DAPT beyond 1 year
  - Account for risks of recurrent ischemia and bleeding simultaneously

- Derived from patients in DAPT trial
  - Those that tolerated DAPT for at least one year
  - Important to review DAPT trial exclusion criteria
    - These patients would not apply to the risk scoring system

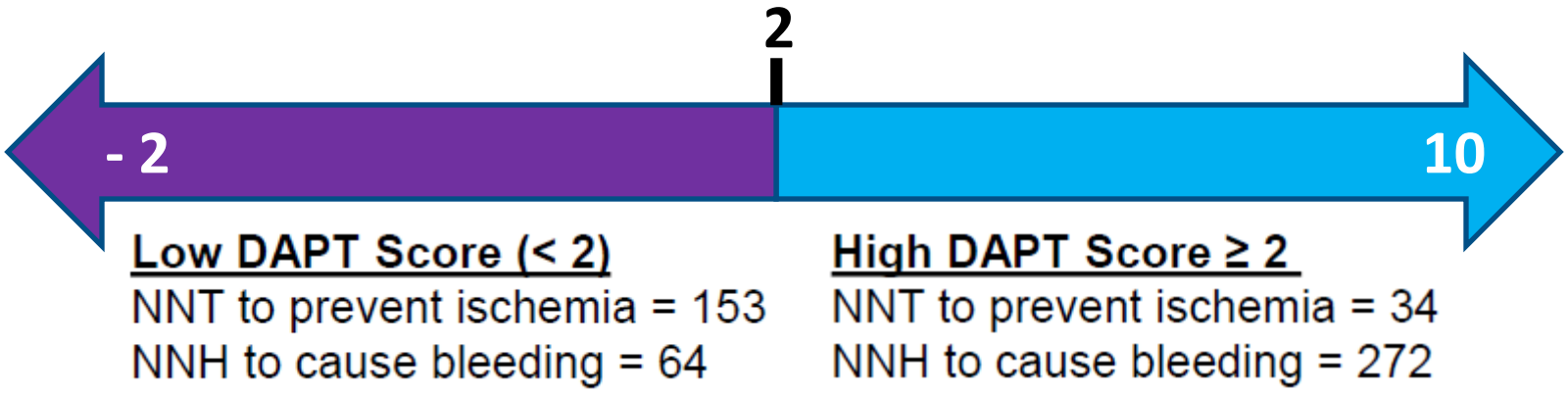
Yeh RW. JAMA 2016;315:1735-1749.

DAPT Score

Variable	Points
Patient Characteristics	
Age:	
≥ 75 years-old	**- 2**
65 – 74	**- 1**
≤ 64	**0**
Diabetes	**1**
Current cigarette smoker	**1**
Prior PCI or prior MI	**1**
CHF or LVEF < 30%	**2**
Index Procedure Characteristic	
MI at presentation	**1**
Vein graft PCI	**2**
Stent Diameter < 3 mm	**1**
TOTAL SCORE	**-2 – 10 points**

Yeh RW. JAMA 2016;315:1735-1749.

DAPT Score



- DAPT score may help identify patients where:
  - Ischemic benefits outweigh the risks of bleeding
  - Bleeding outweighs risk of ischemic events

Yeh RW. JAMA 2016;315:1735-1749.

Aspirin and Warfarin in ACS

Aspirin and Warfarin in ACS

	MACE, %					
	Subjects, n	ASA alone	Warfarin alone	ASA + Warfarin	HR (95%)	p
CHAMP†	5059	31.4		30.9	1.01 (0.9-1.14)	NS
ASPECT-2†	993	9	5	5	0.52 (0.28-0.98)	
APRICOT-2*	274	34		14		<0.01
WARIS-II†	3630	20	16.7	15	0.71 (0.6-0.83)	0.001

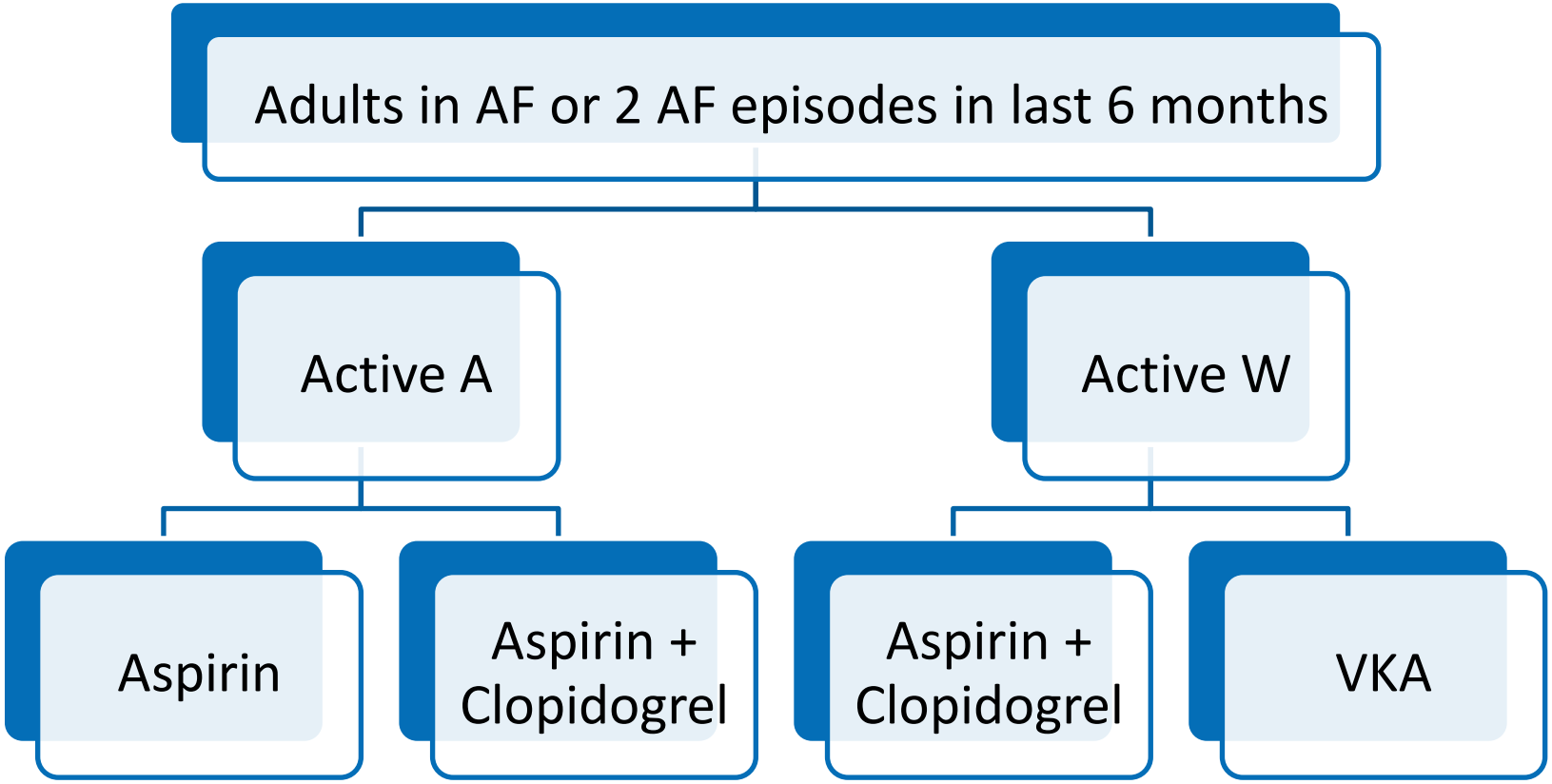
†= death, MI, or stroke; *= Death, reinfarction, revascularization

Fiore LD, et al. Circulation, 2002; 105: 557-63.
Van Es RF, et al. Lancet 2002; 360: 109-13
Brouwer MA, et al. Circulation. 2002; 106: 659-65
Hurlen M, et al. NEJM, 2002; 347(13): 969-74

When complications arise…

- ACS-associated complications
  - Atrial fibrillation
  - Prosthetic Heart Valves
  - Left ventricular thrombus
  - VTE

ACTIVE Trials



1° Outcome: Composite of stroke, non-CNS systemic embolism, MI, CV death

2° Outcome: Stroke; individual outcomes of composite, bleeding, net clinical benefit

Connolly SJ, et al. NEJM 2009; 360: 2066-78

Connolly SJ, et al. Lancet 2006; 367: 1903-12

ACTIVE-A

	Clopidogrel/ASA n (%/yr)	ASA n (%/yr)	RR (95%)	P-Value
Ischemic Outcomes				
Primary Outcome	832 (6.8)	924 (7.6)	0.89 (0.81-0.98)	0.01
Stroke	296 (2.4)	408 (3.3)	0.72 (0.62-0.83)	<0.001
MI	90 (0.7)	115 (0.9)	0.78 (0.59-1.03)	0.08
Non-CNS embolism	54 (0.4)	56 (0.4)	0.96 (0.66-1.4)	0.84
Death	825 (6.4)	841 (6.6)	0.98 (0.89-1.08)	0.69
Bleeding				
Major	251 (2)	162 (1.3)	1.57 (1.29-1.92)	<0.001
Minor	408 (3.5)	175 (1.4)	2.24 (2.03-2.89)	<0.001
Any Bleeding	1014 (9.7)	651 (5.7)	1.68 (1.52-1.85)	0.001
Net Clinical Benefit	968	996	0.97 (0.89-1.06)	0.54

Connolly SJ, et al. NEJM 2009; 360: 2066-78

ACTIVE-W

	Clopidogrel/ASA n (%/yr)	ASA n (%/yr)	RR (95%)	P-Value
Ischemic events				
Primary Outcome	234 (5.6)	165 (3.93)	1.44 (1.18-1.76)	0.0003
Stroke	100 (2.39)	59 (1.4)	1.72 (1.24-2.37)	0.001
MI	36 (0.86)	23 (0.55)	1.58 (0.94-2.67)	0.09
Non-CNS embolism	18 (0.43)	4 (0.1)	4.66 (1.58-13.8)	0.005
Death	159 (3.8)	158 (3.76)	0.93 (0.45-1.94)	0.85
Bleeding Events				
Major	101 (2.42)	93 (2.21)	1.10 (0.83-1.45)	0.53
Minor	568 (13.58)	481 (11.45)	1.23 (1.09-139)	0.0009
Any Bleeding	644 (15.40)	555 (13.21)	1.21 (1.08-1.35)	0.001
Net clinical benefit	316 (7.56)	229 (5.45)	1.41 (1.19-1.67)	<0.0001

Connolly SJ, et al. Lancet 2006; 367: 1903-12

Thrombosis

- No data for treating active thrombosis (LVT or VTE) with antiplatelet therapy alone

Triple Therapy

- Triple therapy is defined as dual-antiplatelet therapy (DAPT) with concomitant oral anticoagulation.

Guidelines

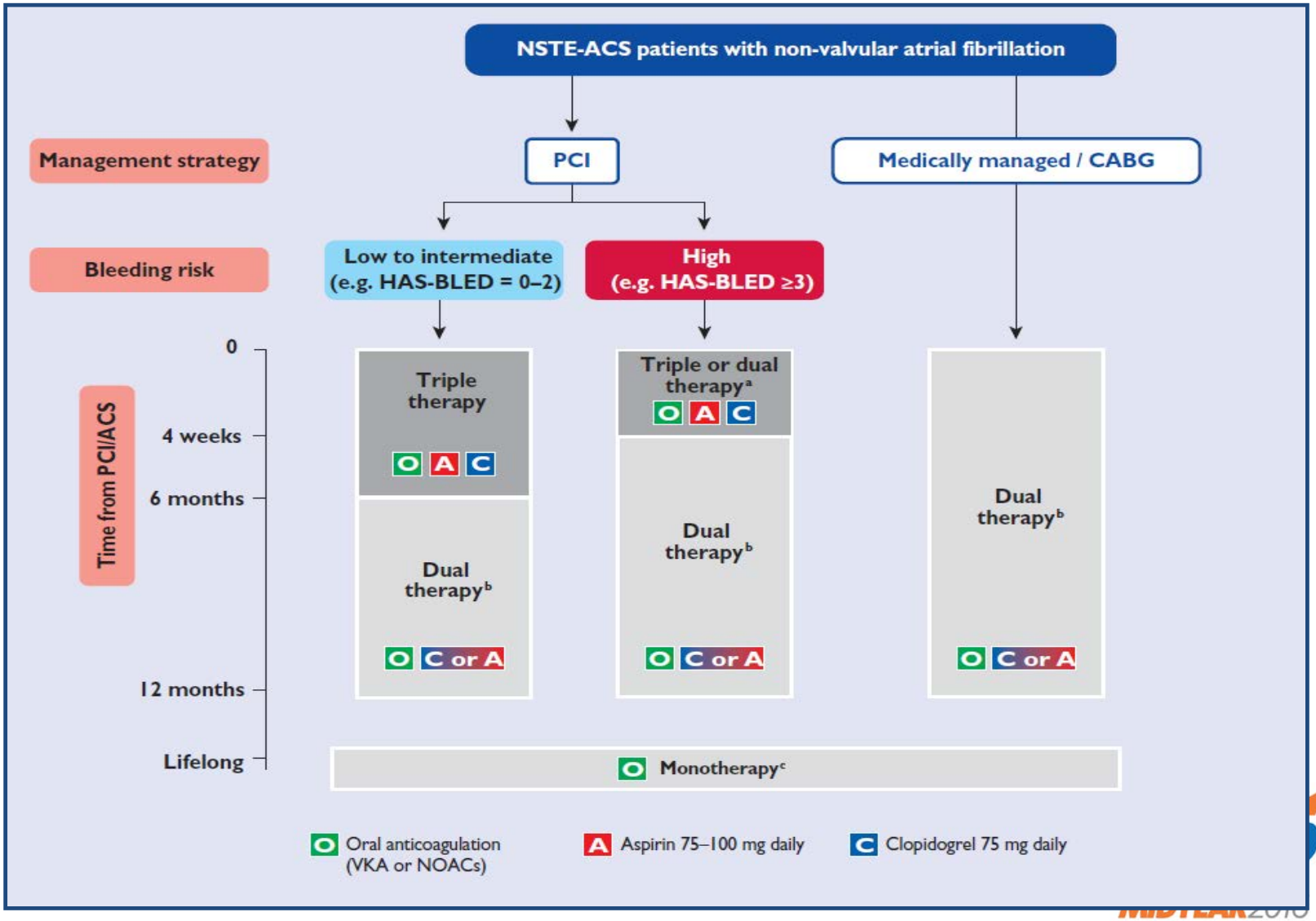
2014 ACC/AHA/HRS Atrial Fibrillation Guidelines

"In patients undergoing PCI, bare-metal stents may be considered to minimized the required duration of DAPT. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding at the site of peripheral arterial puncture. (Level Of Evidence: C)"

"Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA2DS2-VASc score of ≥2, it may be reasonable to use Clopidogrel concurrently with oral anticoagulants but without aspirin. (Level Of Evidence: B)"

January CT, et al. J Am Coll Cardiol, 2014; 64(21): 2246-80

2015 EHS Guidelines for Management of ACS in Patients Presenting Without Persistent STEMI



Roffi M, et al. Eur Heart J, 2016; 34: 267-315

2016 ACC/AHA Focused Update on Duration of DAPT in Patients with CAD

For those patients being treated with triple therapy:

- Assess ischemic/bleeding risk with validated risk predictors (CHA_2DS_2-VASc, HAS-BLED)
- Keep TT duration as short as possible
- Consider warfarin target INR 2.0 – 2.5
- Clopidogrel is the $P2Y_{12}$ inhibitor of choice
- Use low-dose (≤ 100mg daily) Aspirin
- Use concomitant PPI therapy if history of GI bleed or at increased risk of GI bleed

Levine, et al. J Am Coll Cardiol, 2016; 68 (10): 1082-115

Case 1

- AJ is a 68 year-old man with a history of recent NSTE-ACS which was treated with a drug-eluting stent to his LAD who presented to his primary care physicians office complaining of progressively worsening shortness of breath over the past week. An ECG obtained in the office reveals atrial fibrillation and AJ is referred to the hospital for further management. While in the hospital, the team decides to manage AJ with rate control.

Case 1

- Past Medical History:
  - Hypertension
  - Diabetes
  - CAD
    - s/p MI 3 months ago
  - Osteoarthritis
  - Allergic rhinitis
- Social History:
  - Current smoker – 1 pack/day

- Current Medications:
  - Aspirin 81 mg daily
  - Prasugrel 10 mg daily
  - Atorvastatin 80 mg daily
  - Lisinopril 10 mg daily
  - Amlodipine 5 mg daily
  - Metformin 1000 mg BID
  - Sitagliptin 100 mg daily
  - Loratadine 10 mg daily

Case # 2

- BW is an 75 year-old woman with a history of aortic stenosis (AS), who was admitted to the hospital for consideration of valve replacement secondary to repeated heart failure admissions due to AS. She was in the hospital for management of volume overload with intravenous loop diuretics for 5 days.
  - The surgery team is consulted and agrees that she is a candidate for surgical aortic valve replacement
  - BW receives a mechanical aortic valve, and is now out of the ICU and on the step-down floor

Case # 2

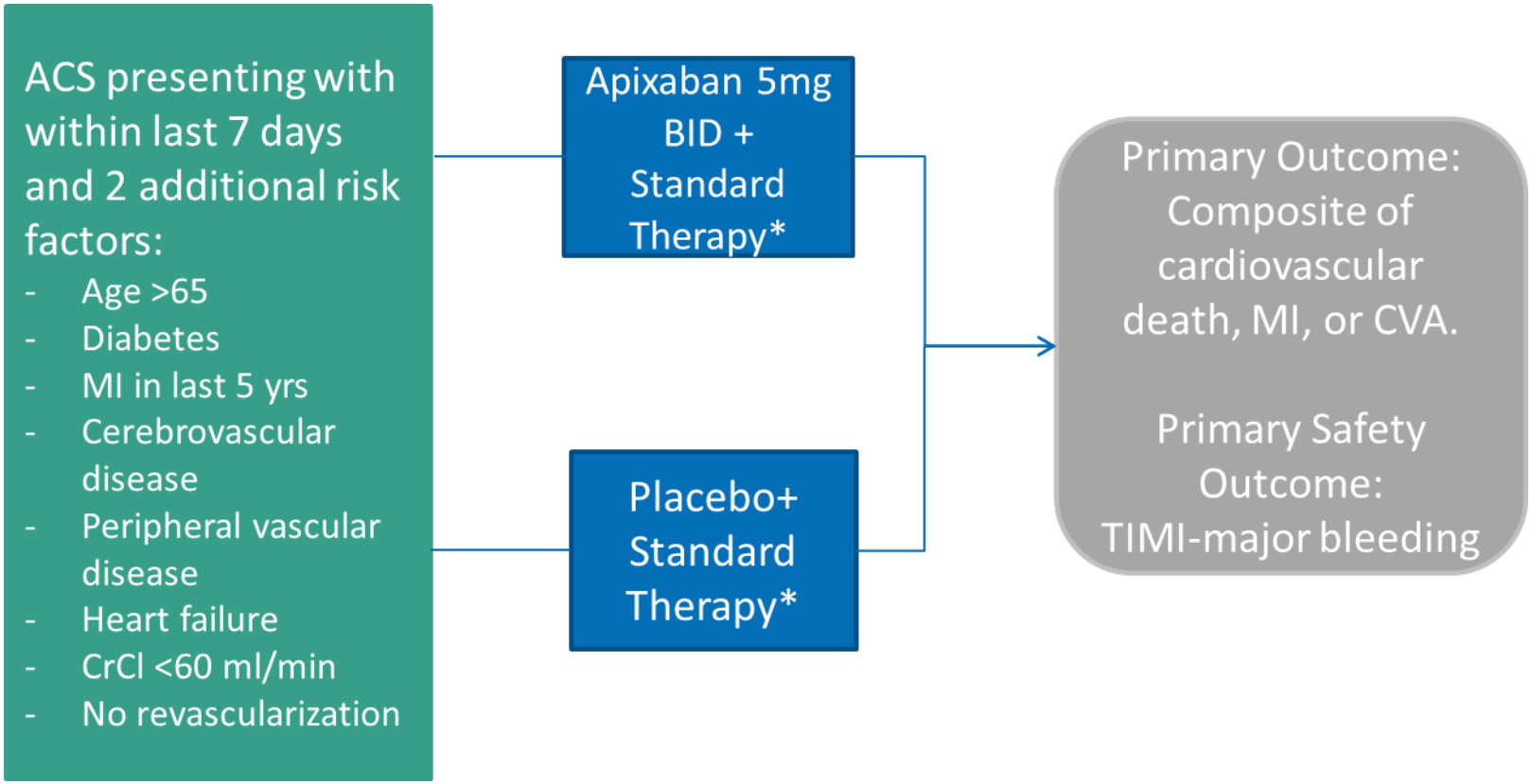
- Past Medical History
  - Hypertension
  - Aortic Stenosis
  - CAD
  - Taxus DES placed in her left circumflex artery 15 months ago
  - Osteoporosis
  - GERD

- Medications:
  - Aspirin 81 mg daily
  - Atorvastatin 40 mg daily
  - Vitamin D 2000 units daily
  - Calcium 500 mg TID
  - Pantoprazole 40 mg daily
  - Clopidogrel 75 mg daily (currently holding)
  - Warfarin dosed to target INR 2-3

Surgical team pages you for recommendations: Clopidogrel

Making the case for triple therapy

APPRAISE-2



Alexander, et al. NEJM, 2011; 365(8): 699-708

APPRAISE-2

- No significant difference in the primary outcome:

	Apixaban N=3705	Placebo N=3687	p-value
CV death, MI, ischemic stroke	7.5	7.9	0.509
CV death, MI, ischemic stroke, UA	9.5	10	0.430
Death	4.2	3.9	0.514
CV death	2.8	2.9	0.754
Myocardial infarction	4.9	5.3	0.509
Ischemic stroke	0.6	0.9	0.145
Unstable angina	2.3	2.4	0.670
Definite stent thrombosis	0.9	1.3	0.150

Alexander, et al. NEJM, 2011; 365(8): 699-708

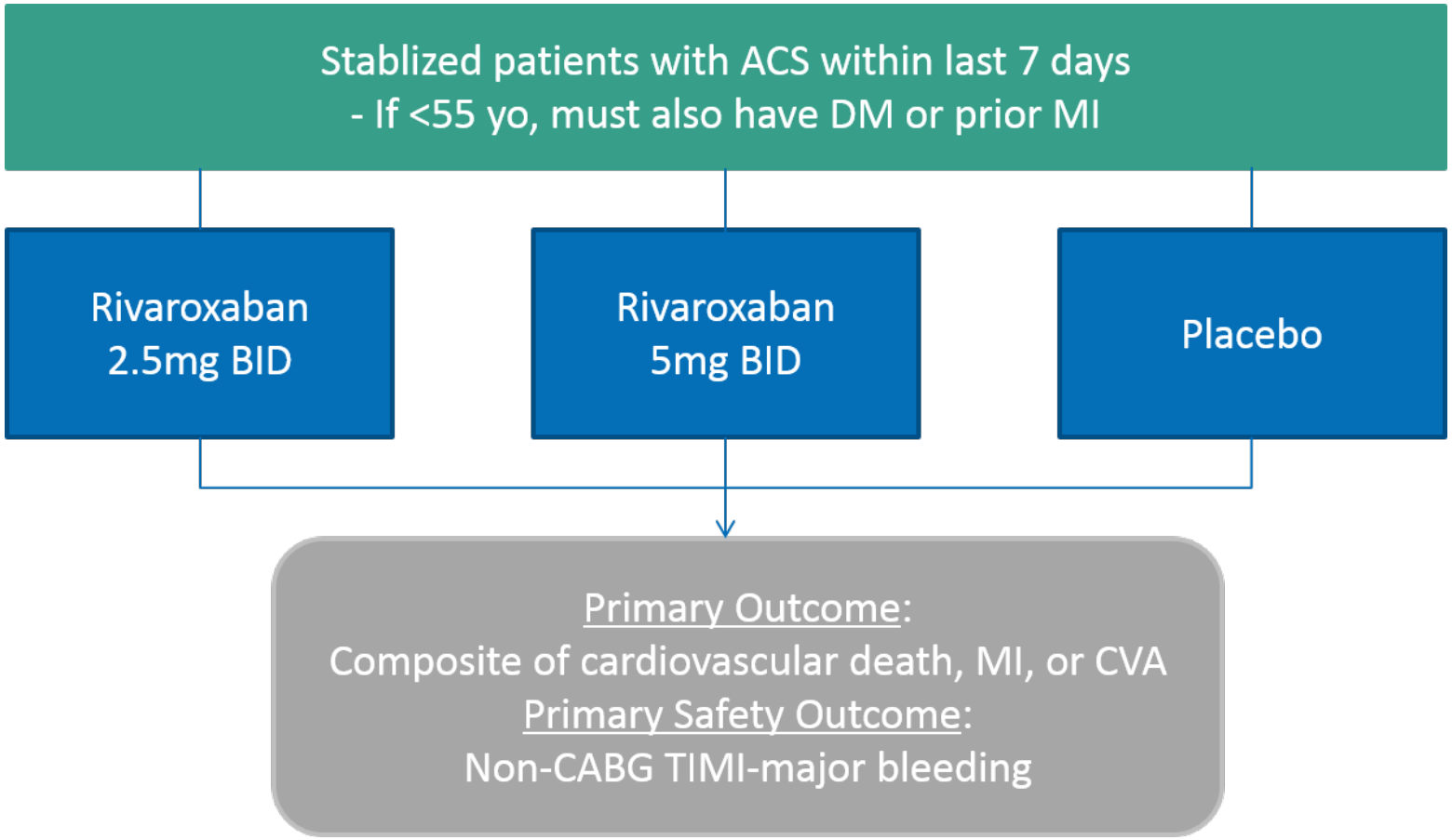
Appraise 2: Major Bleeding

	Apixaban N=3705	Placebo N=3687	p-value
TIMI major	1.3	0.5	0.001
TIMI major or minor	2.2	0.8	<0.001
ISTH major	2.7	1.1	<0.001
ISTH major or clinically relevant non-major	3.2	1.2	<0.001
GUSTO severe	1.0	0.3	0.001
Intracranial	0.3	0.1	0.030

Appraise 2: Conclusions

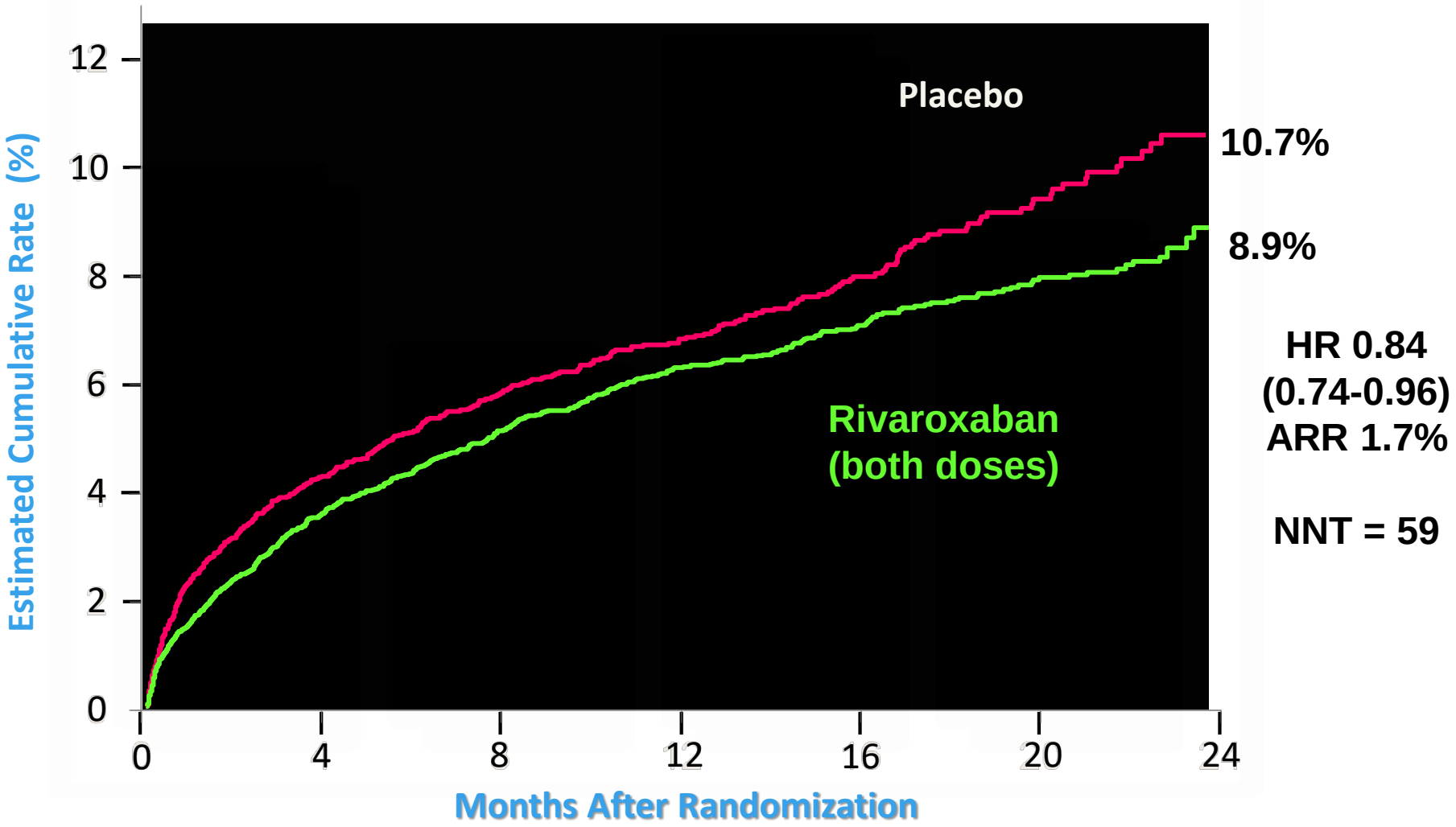
- The addition of apixaban to contemporary antiplatelet therapy increases major bleeding
  - No significant reduction in ischemic events
- Adding an anticoagulant to currently recommended anti-platelet treatment post-ACS should be used cautiously
  - only in patients with clear indications for both an anticoagulant and antiplatelet therapy.
- Further research is needed to explore different antithrombotic combinations and doses that might have a different risk-benefit ratio

ATLAS-ACS 2 – TIMI 51



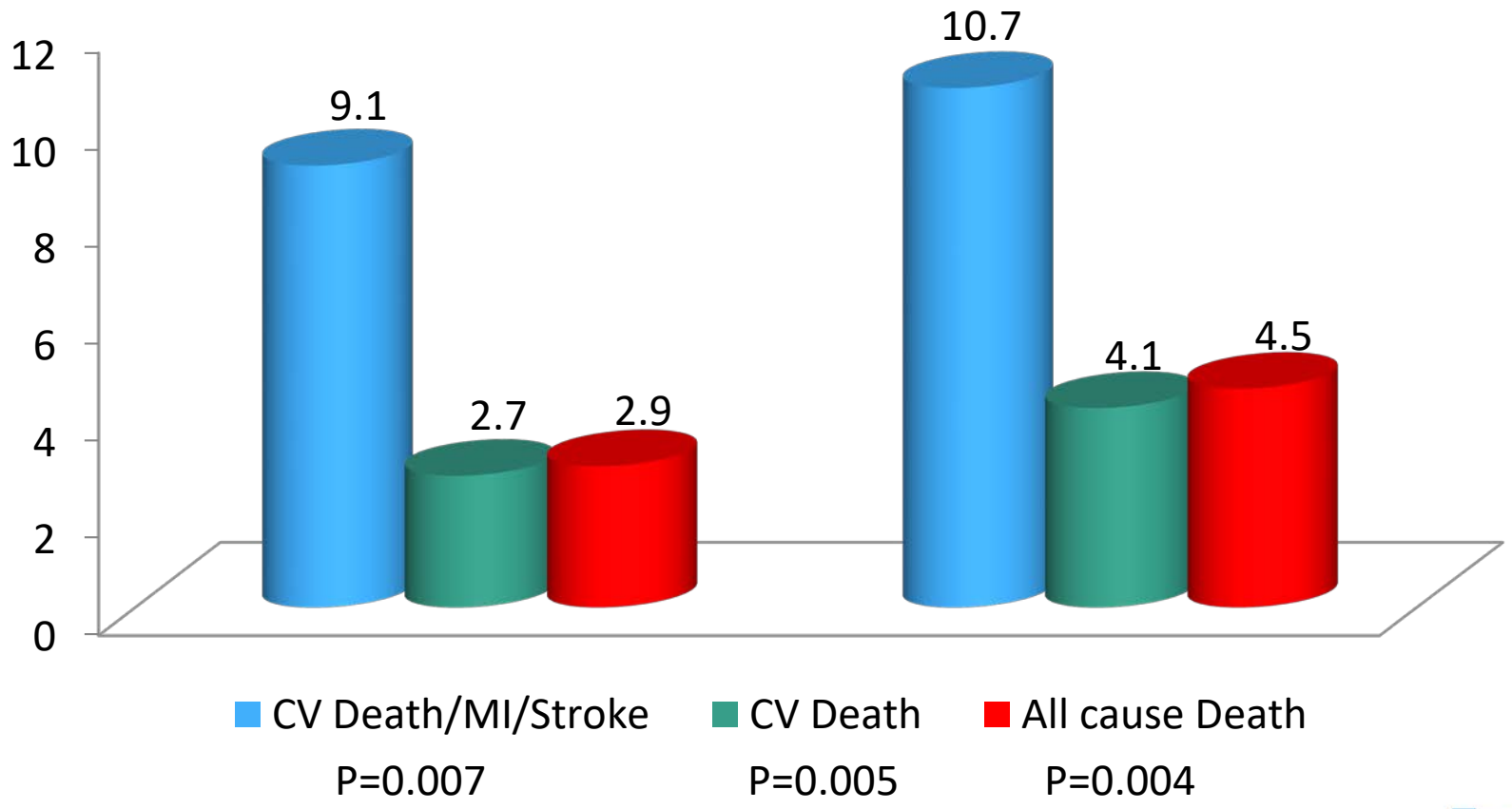
Mega, et al. NEJM, 2012; 366(1): 9-19.

PRIMARY EFFICACY ENDPOINT:



Mega, et al. NEJM, 2012; 366(1): 9-19

Primary Endpoint: 2.5 mg BID Dose



Mega, et al. NEJM, 2012; 366(1): 9-19

ATLAS-ACS 2

	Rivaroxaban			Placebo (N=5113)
	2.5 mg BID (N=5114)	5 mg BID (N=5115)	Combined (N=10,229)	
TIMI major bleeding not associated with CABG	65 (1.8)	82 (2.4)	147 (2.1)	19 (0.6)
TIMI minor bleeding	32 (0.9)	49 (1.6)	81 (1.3)	20 (0.5)
TIMI bleeding requiring medical attention	492 (12.9)	637 (16.2)	1129 (145)	282 (7.5)
Intracranial hemorrhage	14 (0.4)	18 (0.7)	32 (0.6)	5 (0.2)
Fatal bleeding	6 (0.1)	15 (0.4)	21 (0.3)	9 (0.2)

Mega, et al. NEJM, 2012; 366(1): 9-19

ATLAS-ACS 2: Conclusions

- The primary efficacy endpoint of CV death, MI and stroke was reduced when added to standard therapy for both rivaroxaban
- CV and all cause death were reduced in the rivaroxaban 2.5 mg BID group
  - When 2.5 mg PO BID of rivaroxaban was added to ASA + thienopyridine, cardiovascular death was reduced by 38% and all cause death by 36%
- These doses are not currently FDA approved
- Does the dose/intensity of anticoagulation need to be lower with DOACs when combined with DAPT

Danish National Patient Registry

- 2 separate cohort studies using data from the national EMR
  - Patients admitted with first-time MI (2000-2005)
  - Admissions with atrial fibrillation as primary or secondary diagnosis (1997-2006)

- Included subjects >30 yo who received prescriptions for aspirin, clopidogrel, warfarin, or any combination of the three

- 1° Outcome: Bleeding events per patient-year
  - AF study also looked at stroke incidence

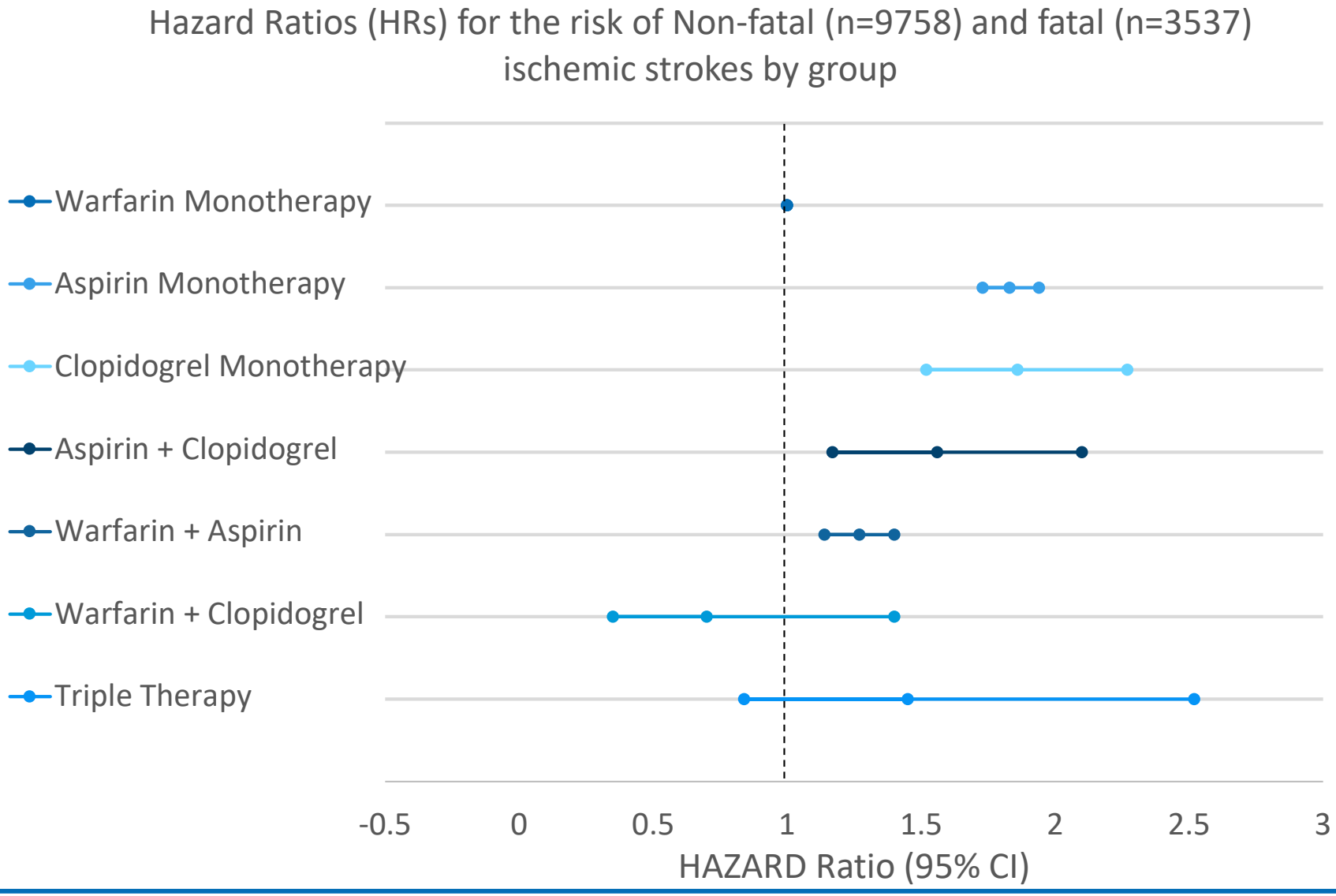
Sorensen R, et al. Lancet. 2009; 374: 1967-74.
Hansen ML, et al. Arch Intern Med. 2010; 170(10): 1433-41

Danish National Patient Registry

	Patients treated for AF		Patients treated for MI	
	Incidence (% per person-yr)	Unadjusted risk ratio (95% CI)	Incidence (% per person-yr)	Unadjusted risk ratio (95% CI)
ASA alone	3.7	0.96 (0.95 – 0.96)	2.6	Reference
Clopidogrel Alone	5.6	1.45 (1.22 – 1.66)	4.6	1.75 (1.75 – 1.76)
VKA alone	3.9	Reference	4.3	1.63 (1.62 – 1.65)
ASA/Clopidogrel	7.4	1.91 (1.59 – 2 21)	3.7	1.43 (1.43 – 1.43)
ASA/VKA	6.9	1.75 (1.71 – 1.79)	5.1	1.94 (1.94 – 1.95)
Clopidogrel/VKA	13.9	3.57 (2.88 – 4.22)	12.3	4.68 (4.64 – 4.74)
Triple Therapy	15.7	4.03 (3.22 – 4.78)	12.0	4.57 (4.55 – 4.61)

Sorensen R, et al. Lancet. 2009; 374: 1967-74.
Hansen ML, et al. Arch Intern Med. 2010; 170(10): 1433-41

Danish National Patient Registry



WOEST

Age 18-80 years old with an indication for PCI and a clear need for ≥ one year oral anticoagulation

- Warfarin, Clopidogrel , ASA
- Warfarin and Clopidogrel

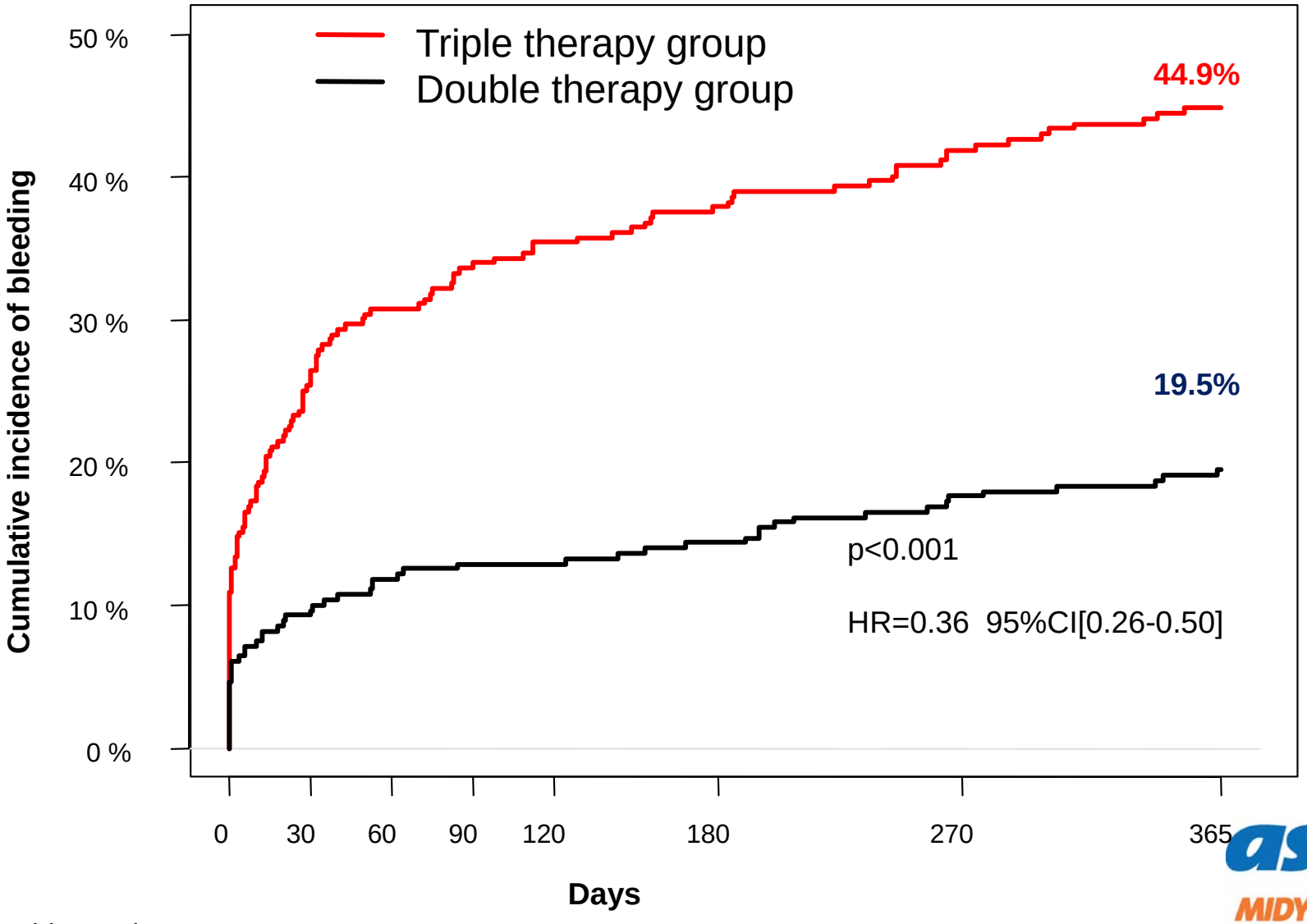
Dewilde, et al. Lancet, 2013; 381: 1107-15

WOEST

- Primary Endpoint:
  - Bleeding rates (TIMI, GUSTO, BARC)
- Secondary Endpoint:
  - Composite of death, MI, stroke, target vessel revascularization, and stent thrombosis
  - Each item individually

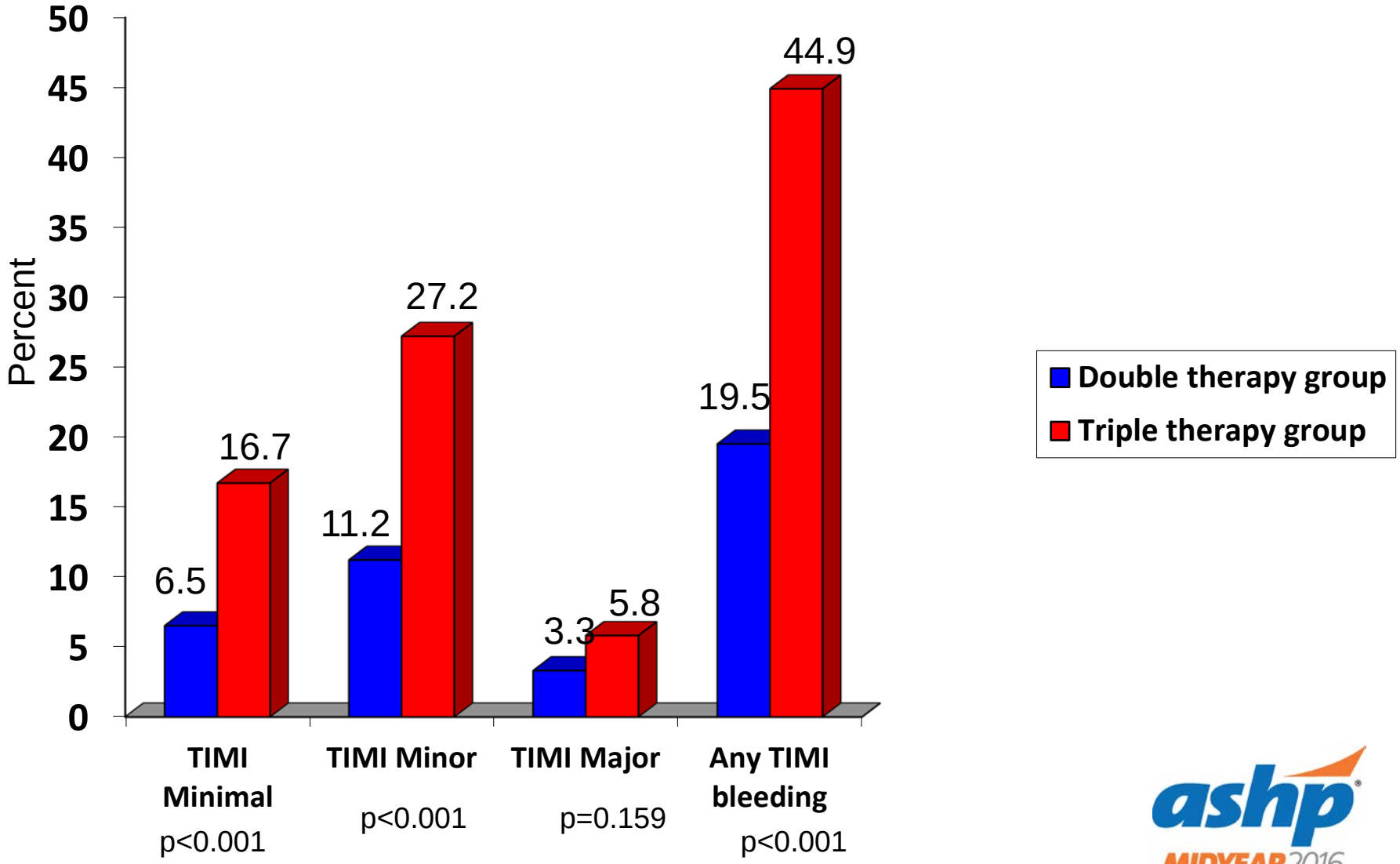
Dewilde, et al. Lancet, 2013; 381: 1107-15

Primary Endpoint: Total number of TIMI bleeding events



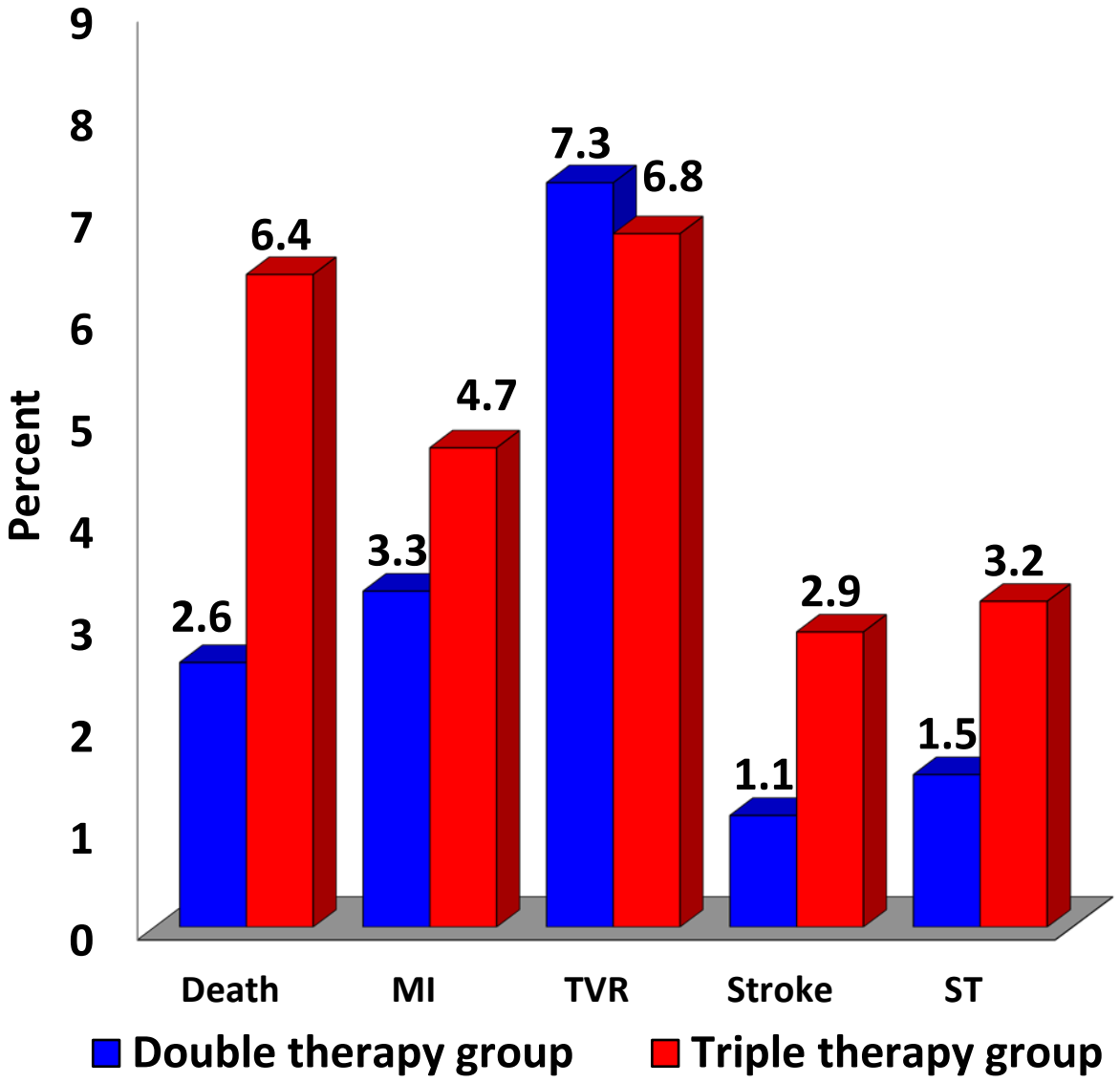
Dewilde, et al. Lancet, 2013; 381: 1107-15

Primary Endpoint: Bleeding events TIMI classification



ashp MIDYEAR2016 Clinical Meeting & Exhibition

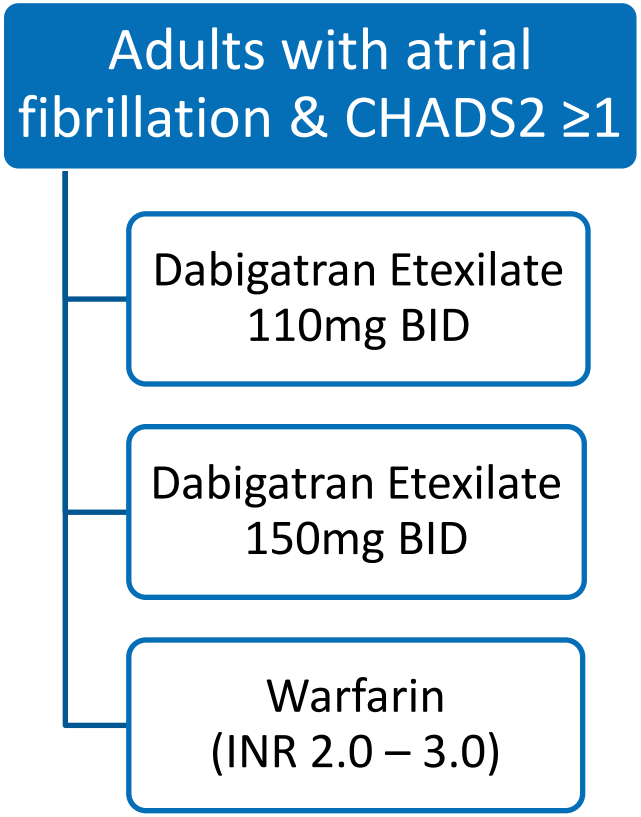
WOEST: Secondary Endpoint



WOEST: Conclusions

- First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting
  - OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy
  - Secondary endpoint was met: with double therapy there is no excess of thrombotic/thromboembolic events
  - Less all-cause mortality with double therapy
- The study was powered to show superiority on the primary bleeding endpoint, but not to show non-inferiority on the secondary endpoint

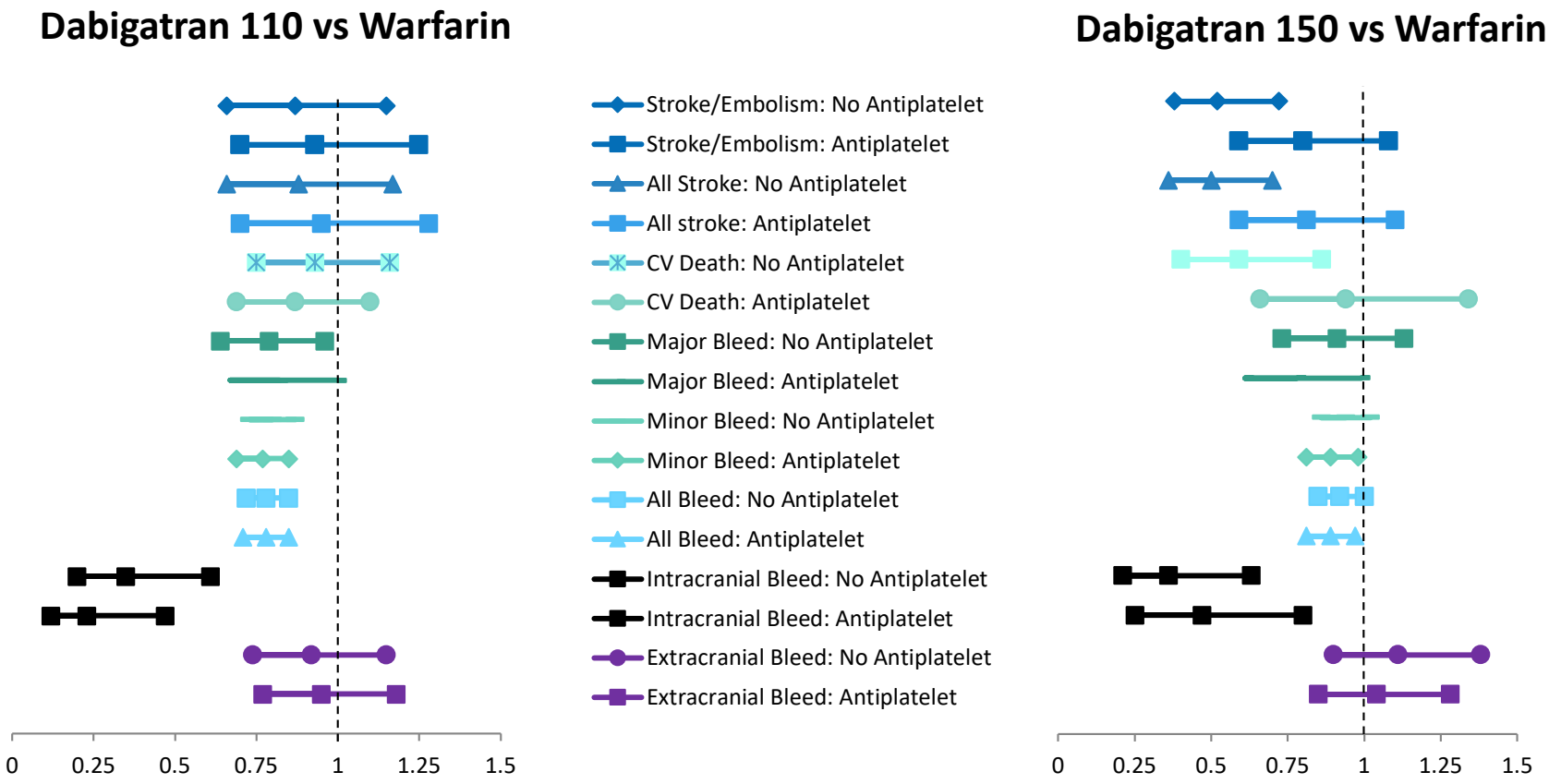
RE-LY Trial



- Use of antiplatelet therapy at any point during trial was 38.4%
  - Aspirin alone = 32%
  - Clopidogrel alone = 1.9%
  - DAPT = 4.5%

Dans AL, et al. Circulation. 2013; 127: 634-40.

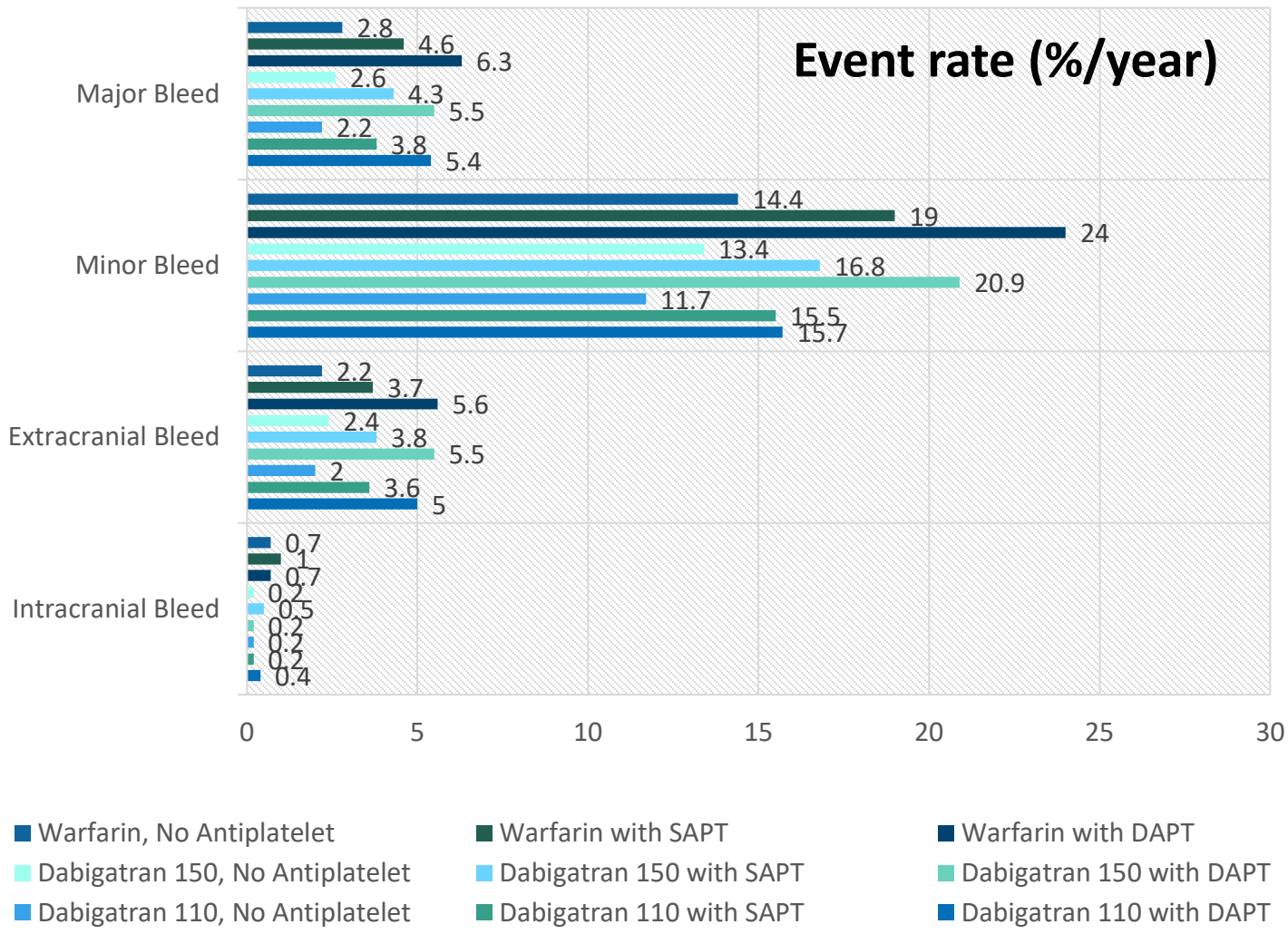
RE-LY Trial



Hazard ratios for stroke and systemic embolism, major bleeding and other outcomes for patients with and without concomitant antiplatelet therapy.

Dans AL, et al. Circulation. 2013; 127: 634-40.

RE-LY Trial



Dans AL, et al. Circulation. 2013; 127: 634-40.

WAR-STENT Registry

- Prospective, multicenter, observational study of patients already on warfarin who are undergoing PCI with stenting
  - Evaluations performed for both the index hospitalization and 12-month follow-up
  - Comparison groups: TT, DT, and DAPT
- Outcomes:
  - Incidence of MACE (CV death, MI, revascularization, stroke, VTE)
  - TIMI major and minor bleeding

Rubboli A, et al. J Invasive Cardiol 2013; 25(4): 170-76
Rubboli A, et al. J Invasive Cardiol 2014; 26(11): 563-9

WAR-STENT Registry

Low thromboembolic risk

- $CHADS_2$ <2
- Bioprosthetic heart valve
- Remote VTE history
- Dilated cardiomyopathy
- LV aneurysm

Non-low thromboembolic risk

- $CHADS_2$ ≥2
- Mechanical heart valve
- Prior cardiogenic embolism
- Intracardiac thrombus
- VTE in last 6 months

Rubboli A, et al. J Invasive Cardiol 2013; 25(4): 170-76
Rubboli A, et al. J Invasive Cardiol 2014; 26(11): 563-9

WAR-STENT Registry

In hospital:

	Overall (n= 411)	Low Thromboembolic Risk (n=31)	Non-Low Thromboembolic Risk (n=380)	p Value
Major adverse cardiovascular events	11 (2.7%)	0	11 (2.9%)	0.71
Death	7 (1.7%)	0	7 (1.8%)	0.44
Non-fatal MI	1 (0.2%)	0	1 (0.2%)	1.00
Stroke	3 (0.7%)	0	3 (0.8%)	1.00
DVT/PE	0	---	---	---
Major bleeding	9 (2.1%)	0	9 (2.3%)	1.00
Minor bleeding	20 (4.8%)	3 (9.6%)	17 (4.4%)	0.18

All access-site bleeding occurred inpatients undergoing PCI via the femoral approach

Rubboli A, et al. J Invasive Cardiol 2013; 25(4): 170-76
Rubboli A, et al. J Invasive Cardiol 2014; 26(11): 563-9

WAR-STENT Registry

- At 12-month follow-up
  - NS difference in MACE, both composite and individually
  - Bleeding:
    - Total bleeding events: no difference across groups
    - MAJOR bleeds: no difference across groups
    - MINOR bleeds: significantly more for the TT group

Rubboli A, et al. J Invasive Cardiol 2013; 25(4): 170-76
Rubboli A, et al. J Invasive Cardiol 2014; 26(11): 563-9

AFCAS Registry

- Prospective, multicenter, observational study of patients with atrial fibrillation who are undergoing PCI with stenting
  - Follow-up performed at months 1, 3, 6, and 12

- Outcomes:
  - MACCE (mortality, MI, revascularization, ST, CVA/TIA)
  - Bleeding (per BARC criteria)
  - Total adverse events (MACCE plus bleeding)

Rubboli A, et al. Clin Cardiol, 2014; 37(6): 357-64

AFCAS Registry

- At baseline, triple therapy was more often prescribed if:
  - Permanent atrial fibrillation at baseline
  - ACS was the indication for PCI
  - Those with a prior history of venous thromboembolism
  - Multiple stents were placed

Rubboli A, et al. Clin Cardiol, 2014; 37(6): 357-64

AFCAS Registry

	TT, n=679	DAPT, n=162	VKA/C, n=73	P
Total MACCE, n (%)	147 (22)	33 (20)	13 (18)	0.72
Stroke/TIA	14 (2)	7 (4)	1 (1)	0.2
Peripheral embolism	6 (1)	1 (0.6)	0	0.69
Myocardial infarction	43 (6)	4 (3)	4 (6)	0.16
Revascularization	54 (8)	10 (6)	7 (10)	0.62
Definite/Probable stent thrombosis	9 (1)	3 (2)	2 (3)	0.6
All cause mortality, n (%)	75 (11)	18 (11)	5 (7)	0.54

Abbreviations: DAPT, dual antiplatelet therapy; MACCE, major adverse cardiac/cerebrovascular events; TIA, transient ischemic attack; TT, triple therapy; VKA, vitamin K antagonist; VKA/C, vitamin K antagonist plus clopidogrel.

Rubboli A, et al. Clin Cardiol, 2014; 37(6): 357-64

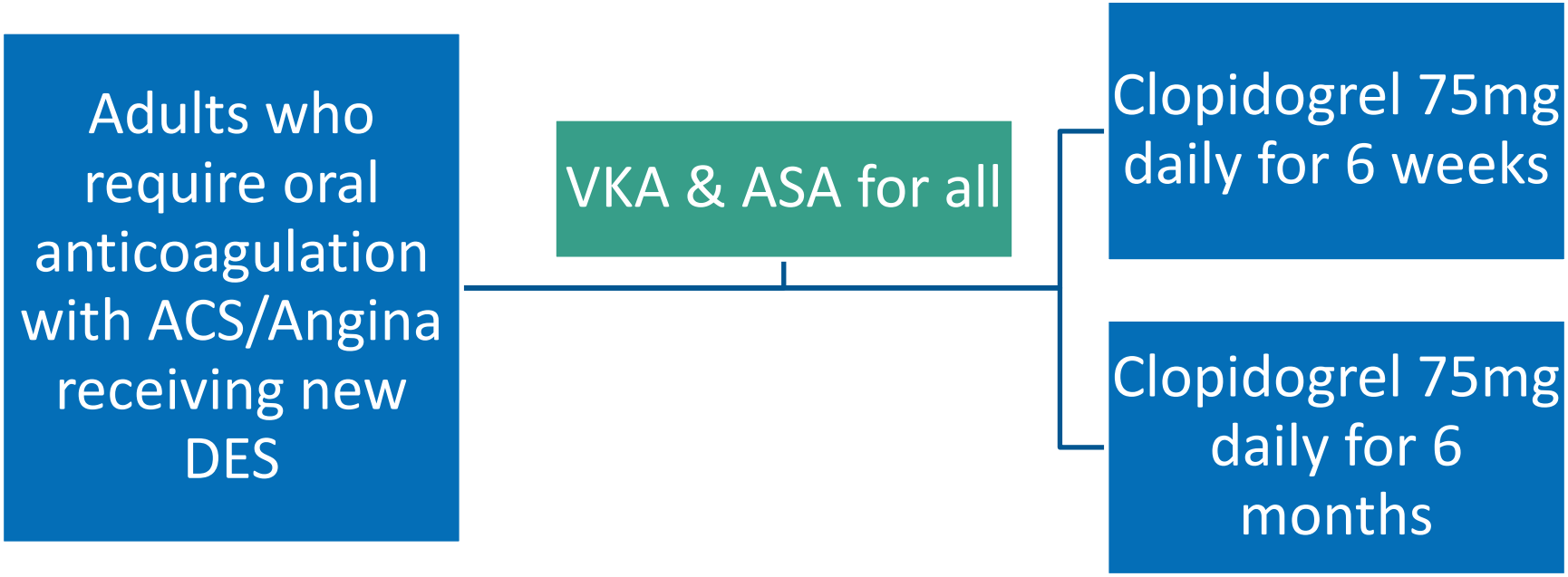
AFCAS Registry

	TT, n=679	DAPT, n=162	VKA/C, n=73	P
Total bleedings, n (%)	119 (18)	33 (20)	12 (16)	0.66
Minor (BARC 2)	51 (8)	13 (8)	7 (10)	0.81
Major, n (%)	69 (10)	20 (12)	5 (7)	0.43
BARC 3a	31 (5)	6 (4)	4 (6)	0.82
BARC 3b	20 (3)	12 (8)	0	0.005
BARC 3c	7 (1)	2 (1)	1 (1)	0.95
BARC 5	10 (2)	0	0	0.17
Total events, n (%) (MACCE + bleeding)	219 (40)	56 (40)	21 (34)	0.67

Abbreviations: BARC, Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; MACCE, major adverse cardiac/cerebrovascular events; TIA, transient ischemic attack; TT, triple therapy; VKA, vitamin K antagonist; VKA/C, vitamin K antagonist plus clopidogrel.

Rubboli A, et al. Clin Cardiol, 2014; 37(6): 357-64

ISAR TRIPLE



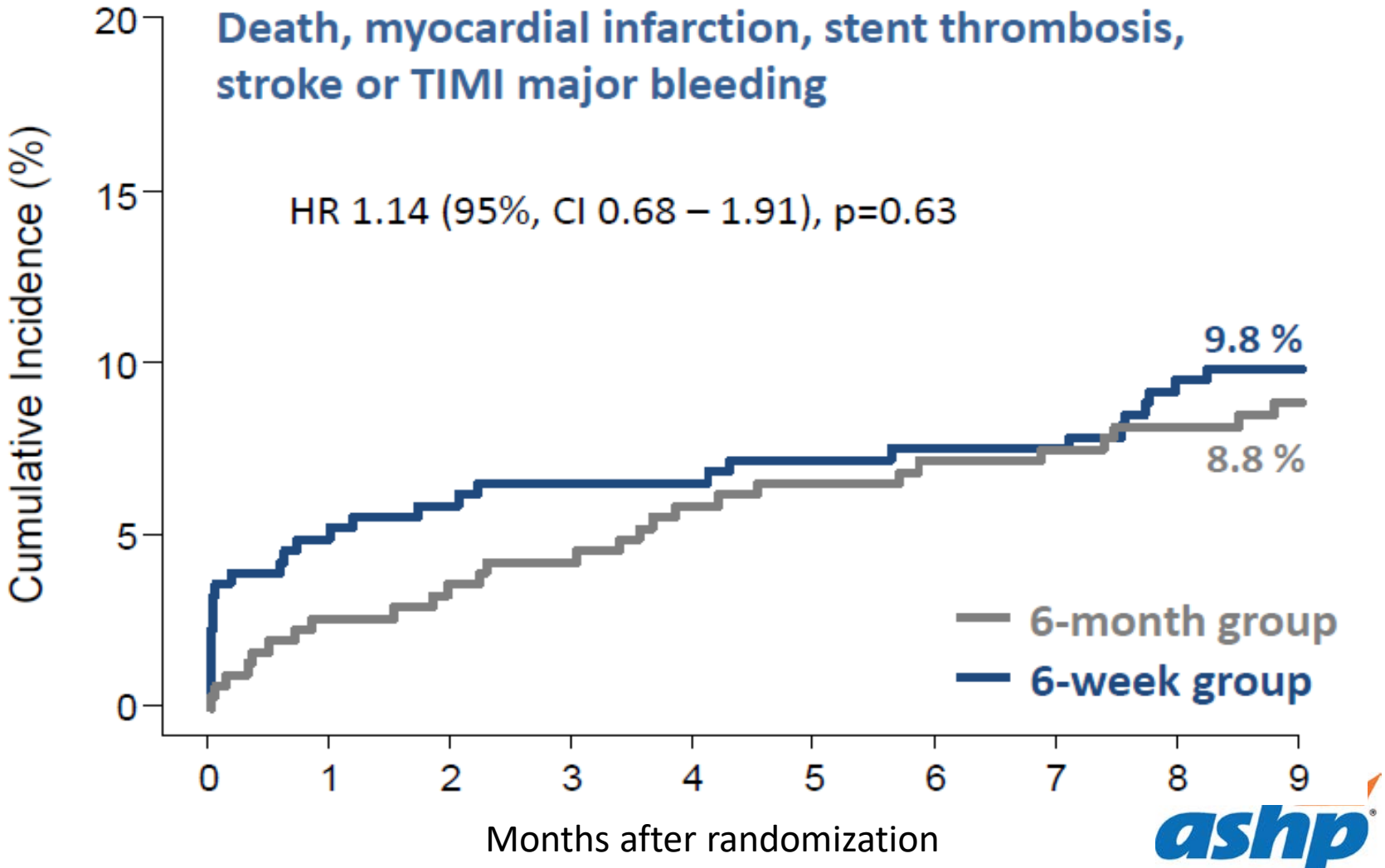
Fiedler, et al. JACC, 2015; 65(16): 1619-29

ISAR TRIPLE

- Primary Endpoint: composite of death, MI, definite ST, stroke, and TIMI-major bleed
- Secondary Endpoints:
  - Composite of ischemic events
  - Composite of bleeding events
  - Each event individually

Fiedler, et al. JACC, 2015; 65(16): 1619-29

ISAR-Triple: Results



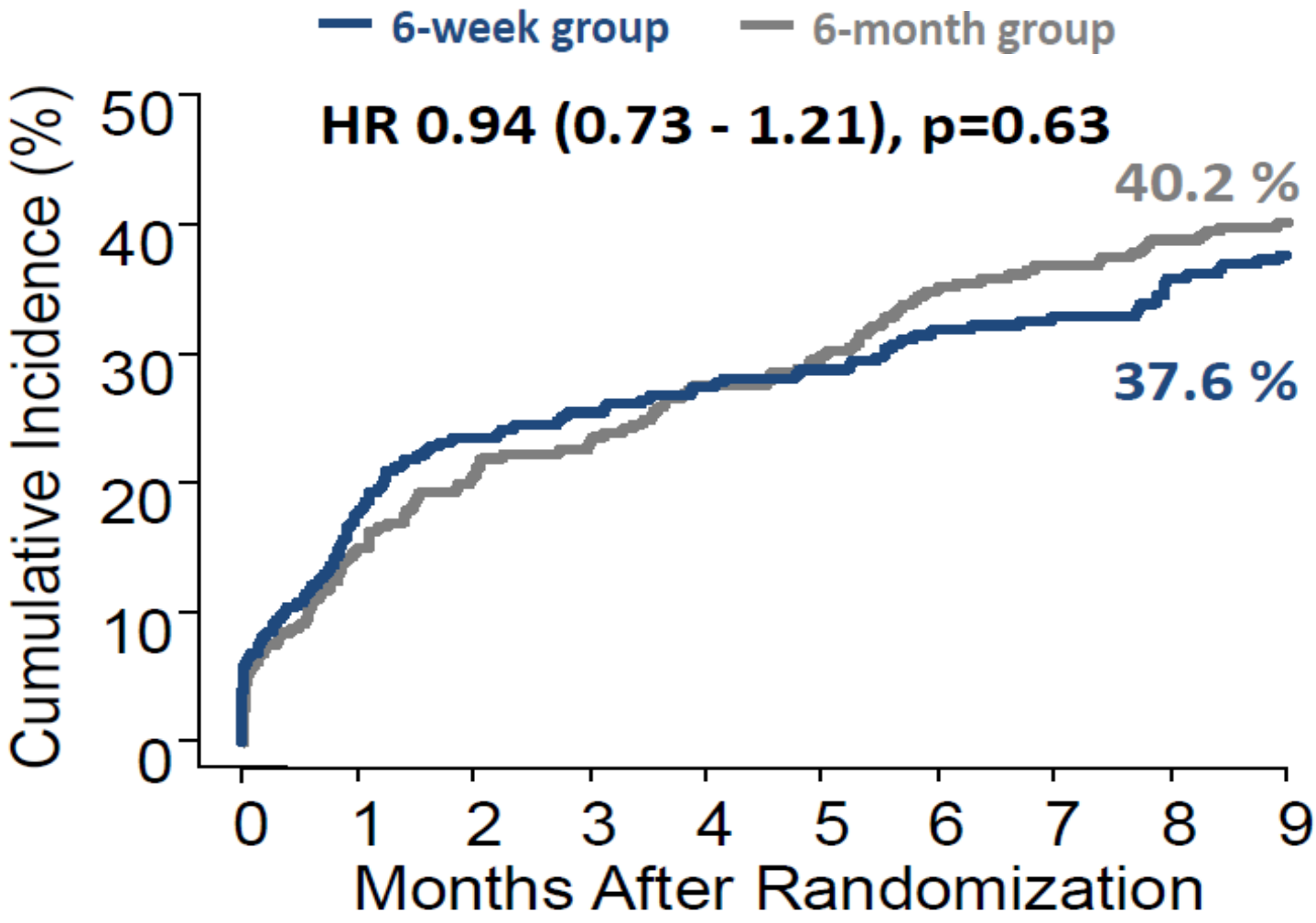
Fiedler, et al. JACC, 2015; 65(16): 1619-29

ISAR-Triple: Results

	6-week group (n=307)	6-month group (n=307)	Hazard Ratio (95% CI)	p value
Death	4%	5.2%	0.75 (0.35 – 1.59)	0.45
Cardiac Death	1.7%	3%	0.56 (0.19 – 1.66)	0.29
MI	2%	0	-	0.03
Definite stent thrombosis	0.7%	0	-	0.50
Stroke	1.3%	2%	0.67 (0.14 – 2.78)	0.75
Ischemic stroke	1%	1.3%	0.75 (0.11 – 4.40)	0.99

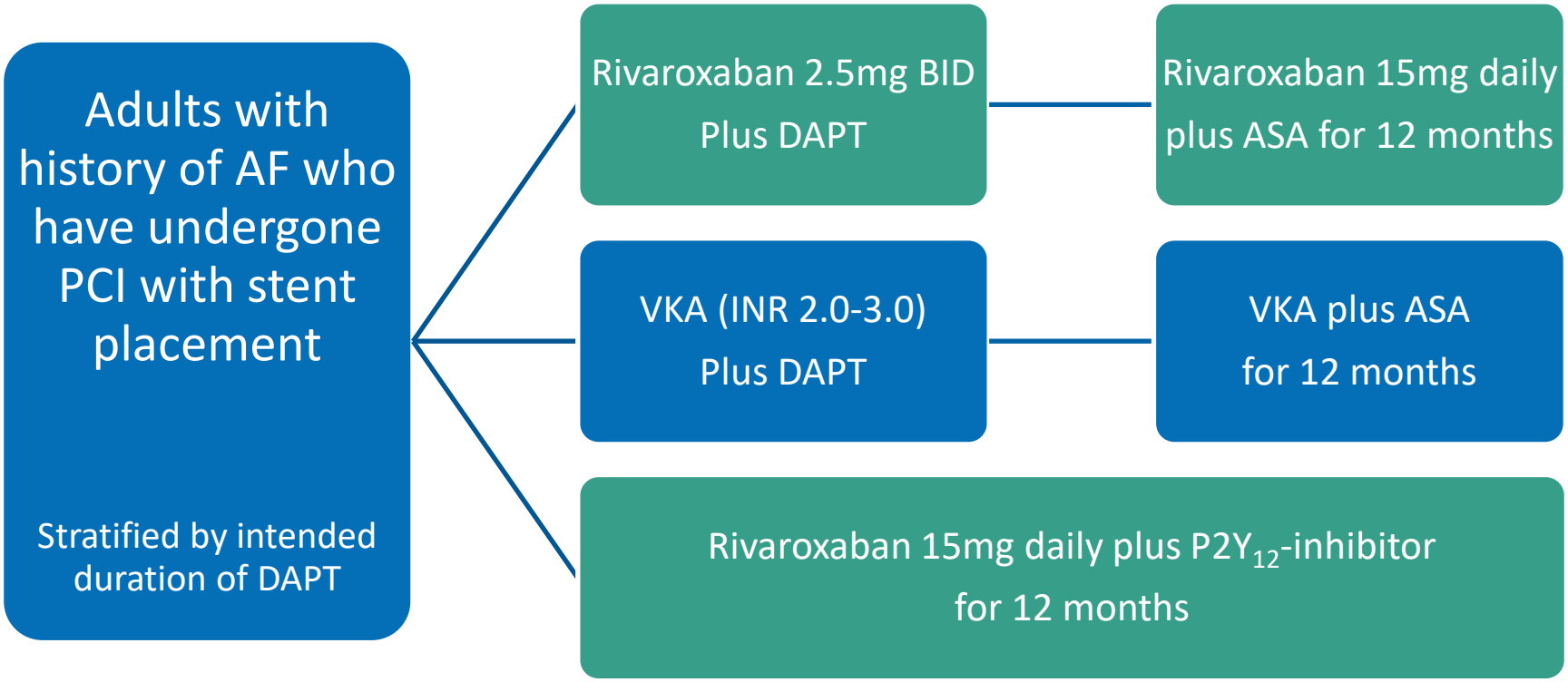
Fiedler, et al. JACC, 2015; 65(16): 1619-29

ISAR-Triple: Major Bleeding (BARC)



Fiedler, et al. JACC, 2015; 65(16): 1619-29

PIONEER AF-PCI : A Study Exploring Two Strategies of Rivaroxaban and One of Oral VKA in Patients with AF who undergo PCI



1° Outcome: TIMI clinically significant bleeding
2° Outcome: time to bleeds, MACE, composite of bleed/MACE events

Gibson CM, et al. Am Heart J. 2015 Apr; 169(4): 472-8.e5.

Questions still remain…

- How long do we keep triple therapy?
- When de-escalating, which OAP do we keep?
- What about $P2Y_{12}$-inhibitors other than Clopidogrel?
- What about the other DOACs?
- What is the long-term risk of thromboembolic complications?

On the horizon…

WOEST-2 Registry

- Prospective, multicenter, non-interventional cohort study involving patients with AF and/or prosthetic heart valves undergoing coronary revascularization
  - Chronic therapy with any oral anticoagulation
  - Receiving any $P2Y_{12}$-inhibitor concomitantly

- Outcomes:
  - Composite of non-fatal MI or stroke, systemic embolism, and cardiovascular death
  - Bleeding episodes requiring hospitalization or change in antithrombotic therapy

https://clinicaltrials.gov/ct2/show/NCT02635230

REDUAL-PCI: Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting

Adults >18 yo with non-valvular atrial fibrillation being treated for ACS/angina with PCI-S (DES or BMS)

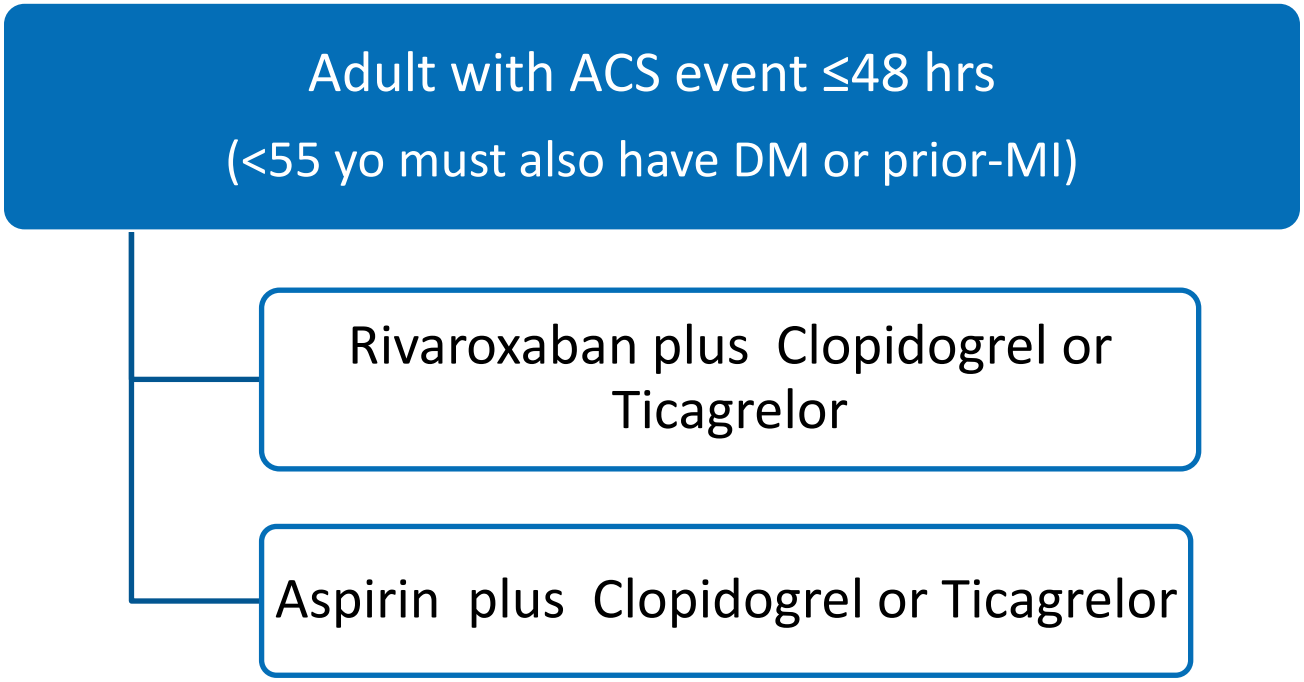
- Dabigatran 110mg BID plus Clopidogrel or Ticagrelor
- Dabigatran 150mg BID plus Clopidogrel or Ticagrelor
- Warfarin (INR 2.0-3.0) plus Aspirin plus Clopidogrel or Ticagrelor

1° Outcome: time to first ISTH major bleed or clinically relevant non-major bleed

2° Outcomes: death, non-CV death, CV death, MI, CVA, SE, ST, composites

https://clinicaltrials.gov/ct2/show/NCT02164864

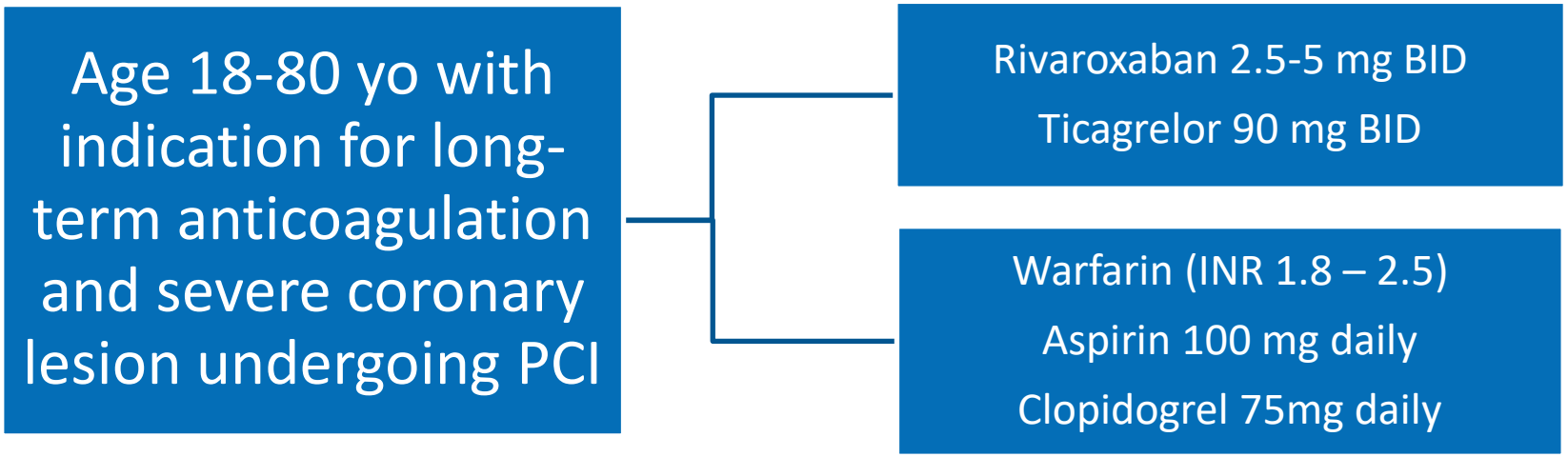
GEMINI-ACS 1: Safety of Rivaroxaban vs ASA in addition to either Clopidogrel or Ticagrelor therapy in participants with ACS



1° Outcome: TIMI clinically significant bleeding events

Povsic TJ, et al. Am Heart J. 2016 Apr; 174: 120-8.

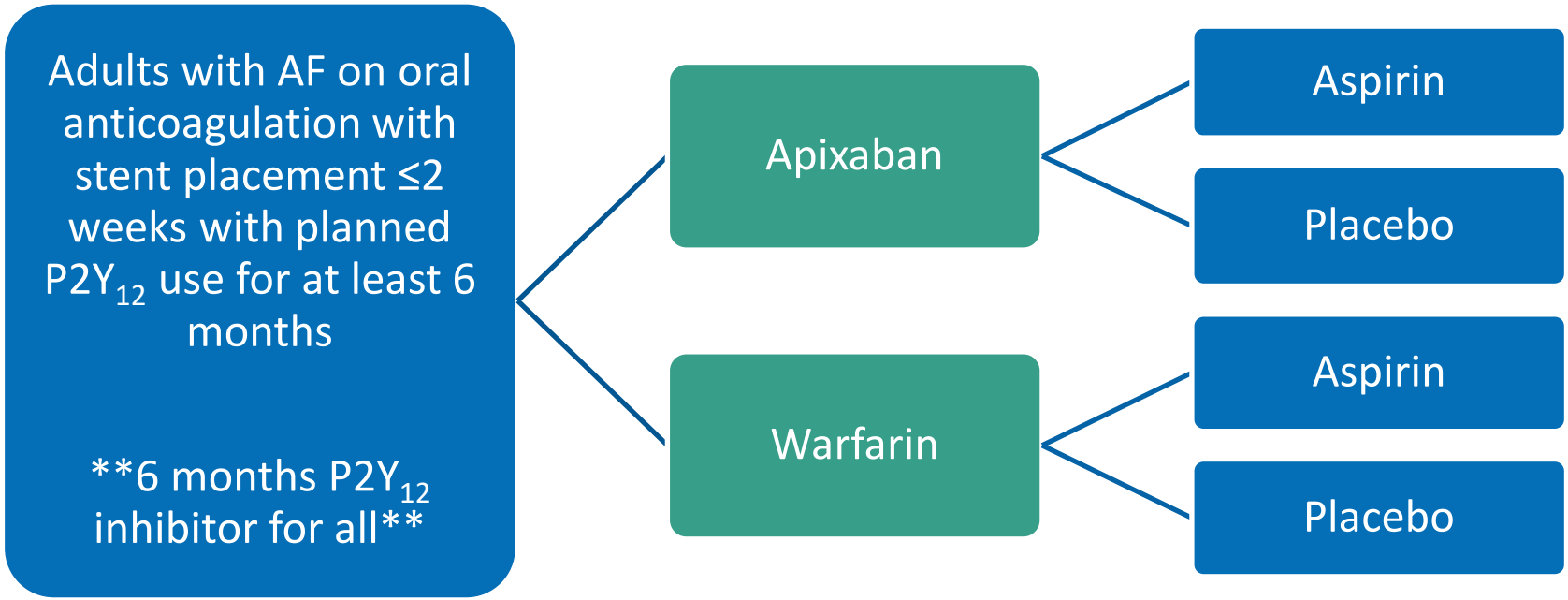
RT-AF: Rivaroxaban in Patients With Atrial Fibrillation and Coronary Artery Disease Undergoing PCI



1° Outcome: Major or clinically relevant bleeding (ISTH)
2° Outcome: Composite of death/MI/ST/Ischemic stroke

Gao F, et al. Contemp Clin Trials. 2015 Jul; 43: 129-32.

AUGUSTUS Trial: Apixaban vs VKA in Patients With AF and ACS or PCI



1° Outcome: ISTH major or clinically non-major bleeding events by group
2° Outcomes: Bleeding, MACE, re-hospitalizations

https://clinicaltrials.gov/ct2/show/NCT02415400

APPROACH-ACS-AF: Apixaban vs Phenprocoumon in Patients with ACS and AF

Adult patients with ACS post-PCI requiring oral anticoagulation for AF/Aflutter ($CHADS_2VASc \geq 2$)

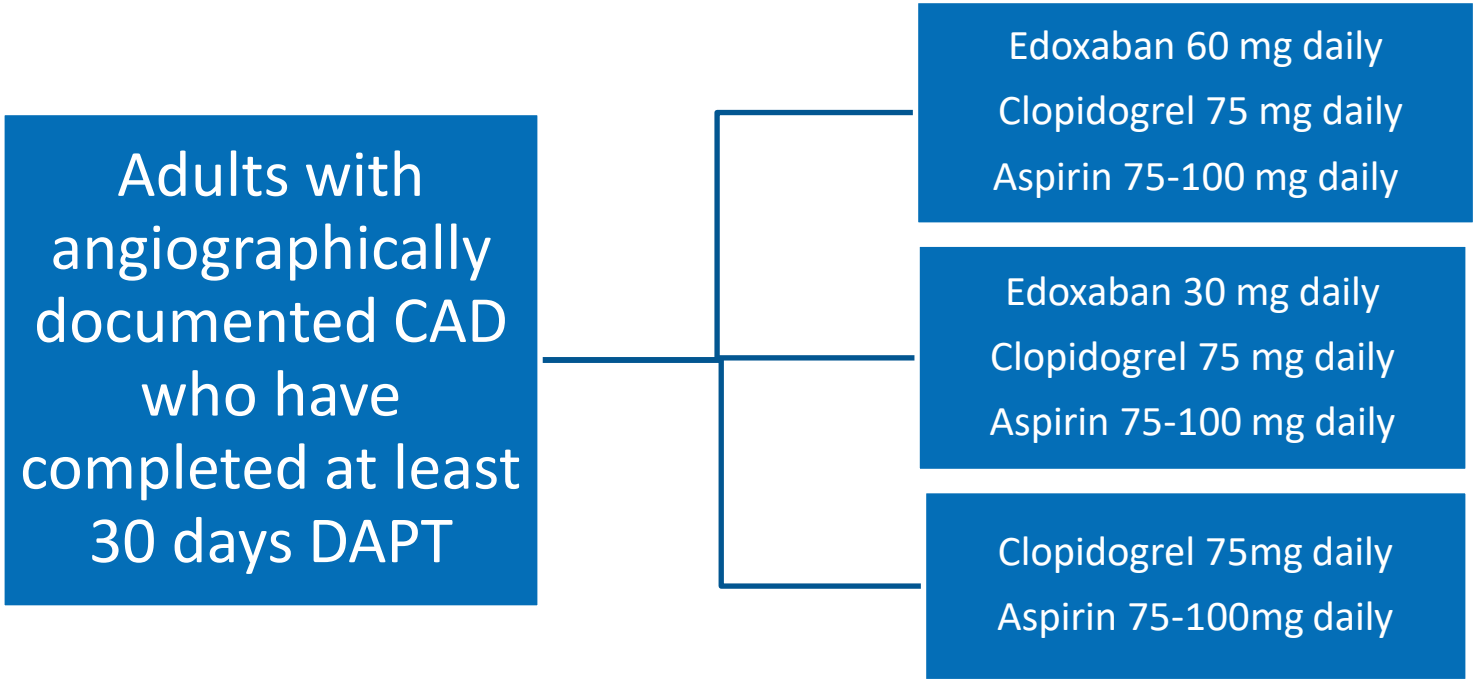
- Apixaban 5mg/d plus Clopidogrel 75mg/d for 6 months
- Phenprocoumon (INR 2.0 – 3.0) , Aspirin, and Clopidogrel
  - HAS-BLED <3: Triple therapy for 6 months
  - HAS-BLED 3: Triple therapy for one month, then Phenprocoumon & Clopidogrel alone

1° Outcome: BARC type ≥2 bleeding

2 ° Outcome: composite of death, MI, ST, CVA/SE; all individually

https://clinicaltrials.gov/ct2/show/NCT02789917

EDOX-APT Trial: Edoxaban in Patients with Coronary Artery Disease on Dual Antiplatelet Therapy with Aspirin and Clopidogrel



1° Outcome: Clot strength +/- Edoxaban, TEG high-dose edoxaban vs DAPT

2° Outcome: Clot strength +/- Aspirin, TEG high-dose edoxaban + DAPT vs high-dose edoxaban + clopidogrel

https://www.clinicaltrials.gov/ct2/show/NCT02567461

Case 1

- AJ is a 68 year-old man with a history of recent NSTE-ACS which was treated with a drug-eluting stent to his LAD who presented to his primary care physicians office complaining of progressively worsening shortness of breath over the past week. An ECG obtained in the office reveals atrial fibrillation and AJ is referred to the hospital for further management. While in the hospital, the team decides to manage AJ with rate control.

Case 1

- Past Medical History:
  - Hypertension
  - Diabetes
  - CAD
    - s/p MI 3 months ago
  - Osteoarthritis
  - Allergic rhinitis
- Social History:
  - Current smoker – 1 pack/day

- Current Medications:
  - Aspirin 81 mg daily
  - Prasugrel 10 mg daily
  - Atorvastatin 80 mg daily
  - Lisinopril 10 mg daily
  - Amlodipine 5 mg daily
  - Metformin 1000 mg BID
  - Sitagliptin 100 mg daily
  - Loratadine 10 mg daily

Case 1: Question # 1

- Which of the following would you recommend to reduce the risk of stroke in AJ?

a) Continue DAPT
b) Discontinue prasugrel
c) Add warfarin
d) Add a DOAC

Case 1: Question # 2

- AJ chooses to be placed on anticoagulation therapy. Which of the following would you suggest at this time?

a) Discontinue aspirin, add warfarin
b) Switch prasugrel to clopidogrel, add warfarin
c) Continue aspirin, prasugrel, add warfarin
d) Continue aspirin, prasugrel, add DOAC
e) Switch prasugrel to clopidogrel, add DOAC

Case # 2

- BW is an 75 year-old woman with a history of aortic stenosis (AS), who was admitted to the hospital for consideration of valve replacement secondary to repeated heart failure admissions due to AS. She was in the hospital for management of volume overload with intravenous loop diuretics for 5 days.
  - The surgery team is consulted and agrees that she is a candidate for surgical aortic valve replacement
  - BW receives a mechanical aortic valve, and is now out of the ICU and on the step-down floor

Case # 2

- Past Medical History
  - Hypertension
  - Aortic Stenosis
  - CAD
  - Taxus DES placed in her left circumflex artery 15 months ago
  - Osteoporosis
  - GERD

- Medications:
  - Aspirin 81 mg daily
  - Atorvastatin 40 mg daily
  - Vitamin D 2000 units daily
  - Calcium 500 mg TID
  - Pantoprazole 40 mg daily
  - Clopidogrel 75 mg daily (currently holding)
  - Warfarin dosed to target INR 2-3

Surgical team pages you for recommendations: Clopidogrel

Case 2: Question # 1

- How would you manage BW's antithrombotic therapy?

a) Continue triple therapy (aspirin, clopidogrel, warfarin)
b) Discontinue clopidogrel
c) Change warfarin to DOAC (aspirin, clopidogrel, DOAC)
d) Discontinue aspirin

Key Takeaways

- Key Takeaway #1
  - Triple therapy with DAPT + OAC increases bleeding, but is often unavoidable in clinical practice
- Key Takeaway #2
  - DAPT is recommended in patients with recent ACS and stent placement, and OAC alone does not provide protection
- Key Takeaway #3
  - OAC is superior to DAPT in stroke prevention in AF
- Key Takeaway # 4
  - Dual therapy options with either single antiplatelet therapy plus OAC (either warfarin or DAOC) have potential, but ongoing clinical trial data will clarify the risks and benefits of this strategy compared with triple therapy

Questions?