Triple Therapy: A review of the evidence in acute coronary syndrome

Stephanie Kling, PharmD, BCPS

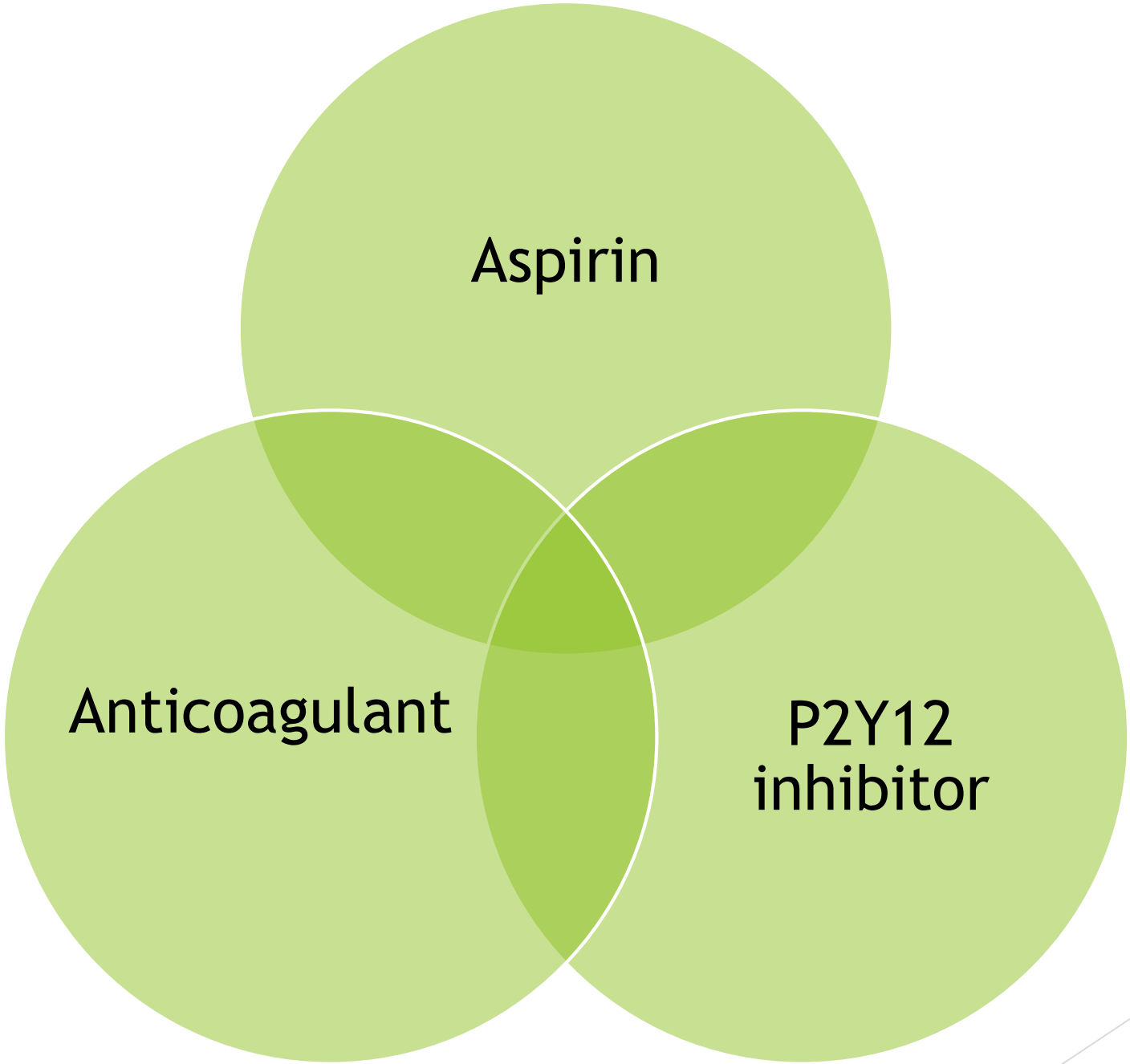
Sanford Health

Objectives

1. Describe how the presented topic impacts patient outcomes.
2. Review evidence based guidelines and best practices described.
3. Identify two clinical endpoints of the presented topic.
4. Recommend therapeutic means to achieve clinical endpoints.

Outline

- Background
- Current Literature
  - Warfarin within TT
  - NOAC within TT
  - Ticagrelor/Prasugrel within TT
- Future studies


Aspirin
Anticoagulant
P2Y12 inhibitor

Abbreviations

- TT= triple therapy
- PCI= percutaneous coronary intervention
- MACCE= major adverse cardiovascular and cerebrovascular events
- MI= myocardial infarction
- CABG= coronary artery bypass graft
- NOAC= novel oral anticoagulant
- BARC = bleeding academic research consortium
- TIMI= thrombolysis in myocardial infarction
- GUSTO= global use of strategies to open occluded arteries
- DES= drug eluting stent
- BMS = bare metal stent
- CABG= coronary artery bypass graft
- Hgb= hemoglobin
- ISTH= international society on thrombosis and heamostasis

BARC Definitions

Type	Definition
Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek treatment
Type 2	Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, hospitalization, or treatment by a health care professional
Type 3	a. Overt bleeding plus hemoglobin drop of 3-5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus hemoglobin drop of < 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
Type 4	CABG-related bleeding within 48 hours
Type 5	a. Probable fatal bleed b. Definite fatal bleeding (overt or autopsy or imaging confirmation)

TIMI Definitions

Type	Definition
Major	Intracranial hemorrhage ≥ 5 g/dL decrease in the hemoglobin concentration ≥ 15% absolute decrease in hematocrit
Minor	Observed blood loss: ≥ 3g/dL decrease in the hemoglobin concentration ≥10% decrease in the hematocrit No observed blood loss: ≥4 g/dL decrease in the hemoglobin concentration ≥12% decrease in hemaotcrit
Minimal	Any clinically overt sign of hemorrhage associated with a < 3 g/dL decrease in the hemoglobin concentration or < 9% decrease in the hematocrit

GUSTO Definitions

Type	Definition
Severe or life-threatening	Intracranial hemorrhage Bleeding that causes hemodynamic compromise and intervention
Moderate	Bleeding that requires blood transfusion but does not lead to hemodynamic instability
Mild	Bleeding that does not meet criteria for severe or moderate bleeding

ISTH Assessment Tool

Symptoms	Criteria	Normal Range	Major
Epistaxis Cutaneous symptoms Bleeding from minor wounds Oral cavity symptoms GI Bleeding Hematuria Tooth extraction Surgery Menorrhagia Post-partum hemorrhage Muscle hematoma Hemarthrosis CNS bleeding Other bleeding	Score 0-4 for each symptom based on specific criteria, such as not needing treatment, needing consultation from health care professional, requiring transfusions, surgery, etc.	< 4 adult males < 6 adult females < 3 children	Fatal bleed And/or Symptomatic bleeding in a critical area or organ And/or Bleeding causing fall in hemoglobin level of 2 g/dL or more, leading to transfusion of 2 or more units of blood

Background

- Approximately 10% of the nearly 1 million patients who undergo PCI in US each year have an indication for chronic oral anticoagulation therapy
- Dual antiplatelet therapy (DAPT) is mainstay treatment for secondary prevention of MACE in patients who have survived acute coronary syndrome and/or have received a stent
- Triple therapy results in at least a 2- to 3-fold increase in bleeding complications

Guidelines

- 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease
  - Assess ischemic and bleeding risks using validated risk predictors
  - Keep triple therapy duration as short as possible
  - Consider target INR 2.0-2.5
  - Clopidogrel is P2Y12 inhibitor of choice
  - Use low dose aspirin
  - PPI should be used in patients with history of GI bleed and are reasonable in patients with increased risk of GI bleed

Levine GN et al. Journal of the American College of Cardiology 2016; 68 (10): 1082-1115.

European Consensus Document

- Newer generation DES preferable over BMS, particularly in patients at low risk of bleeding
- New generation p2y12 inhibitors should not be used in antithrombotic combination therapy with anticoagulants
- NOACs and VKAs are interchangeable and patients already receiving a NOAC should not be switched to VKA if a NOAC is used in combination.
  - Use lower doses: dabigatran 110 mg BID, rivaroxaban 15 mg daily, apixaban 2.5 mg BID
- VKA: INR 2.0-2.5

Rohla et al . European Heart Journal-Cardiovascular Pharmacotherapy 2015: 1: 191-197.

Warfarin

Use of Clopidogrel with or without Aspirin in Patients Taking Oral Anticoagulant Therapy and Undergoing Percutaneous Coronary Intervention: an Open-Label, Randomized, Controlled Trial

Dewilde WJM et al. Lancet 2013; 381: 1107-1115.

WOEST

What is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing

WOEST

N= 573

Warfarin + clopidogrel

N= 284

Warfarin + clopidogrel + aspirin

N= 289

WOEST

Inclusion

- Age 18-80
- Long term indication for oral anticoagulation treatment
- Severe coronary lesion with indication for PCI

Exclusion

- History of intracranial bleeding
- Cardiogenic shock
- Peptic ulcer in previous 6 months
- Thrombocytopenia
- TIMI major bleed in past 12 months
- Contraindication to study medications

WOEST

Primary Outcome	Occurrence of any bleeding episode during 1 year follow-up (TIMI, GUSTO, and BARC)
Secondary Outcomes	• Composite of death, MI, stroke, target-vessel revascularization, and stent thrombosis • Separate assessment of each component of primary and secondary

WOEST

	Warfarin + clopidogrel	Triple therapy	Hazard Ratio and P-Value
Any bleeding	54 (19.4%)	126 (44.4%)	0.36 (95% CI 0.26-0.50) P < 0.0001
Composite of death, MI, stroke, target-vessel revascularization, and stent thrombosis	31 (11.1%)	50 (17.6%)	0.6 (95% CI 0.38-0.94) P 0.025

WOEST

- Risk of bleeding is high using triple oral antithrombotic therapy
- At 1 year oral anticoagulation was being used by 92.5% of patients in the double-therapy group and 91.2% of the triple-therapy group
- Use of clopidogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events

Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation

Fiedler et al. Journal of the American College of Cardiology 2015; 65(16): 1619-1629.

ISAR-TRIPLE

ISAR-TRIPLE

Aspirin + clopidogrel + VKA

N= 614

6 weeks

N= 307

6 months

N= 307

ISAR-TRIPLE

Inclusion

- Age 18 and above
- Long term indication for oral anticoagulation treatment (1 year or more)
- Receiving DES for stable angina or ACS

Exclusion

- Previous stent thrombosis,
- DES left main stem
- Active bleeding
- History of intracranial bleeding

ISAR-TRPLE

Primary Outcome	Composite of death, MI, definite stent thrombosis, stroke, or TIMI major bleeding at 9 months after randomization
Secondary Outcomes	• Incidence of ischemic complications (cumulative incidence of cardiac death, MI, definite stent thrombosis, or ischemic stroke or bleeding complications (TIMI major) • Each individual component of primary and secondary endpoints

ISAR-TRIPLE

	6 weeks	6 months	Hazard Ratio and P-Value
Primary Outcome	30 (9.8%)	27 (8.8%)	1.14 (95% CI 0.68-1.91) P= 0.63
Secondary Outcome	12 (4%)	13 (4.3%)	0.93 (95% CI 0.43-2.05) P=0.87

ISAR-TRIPLE

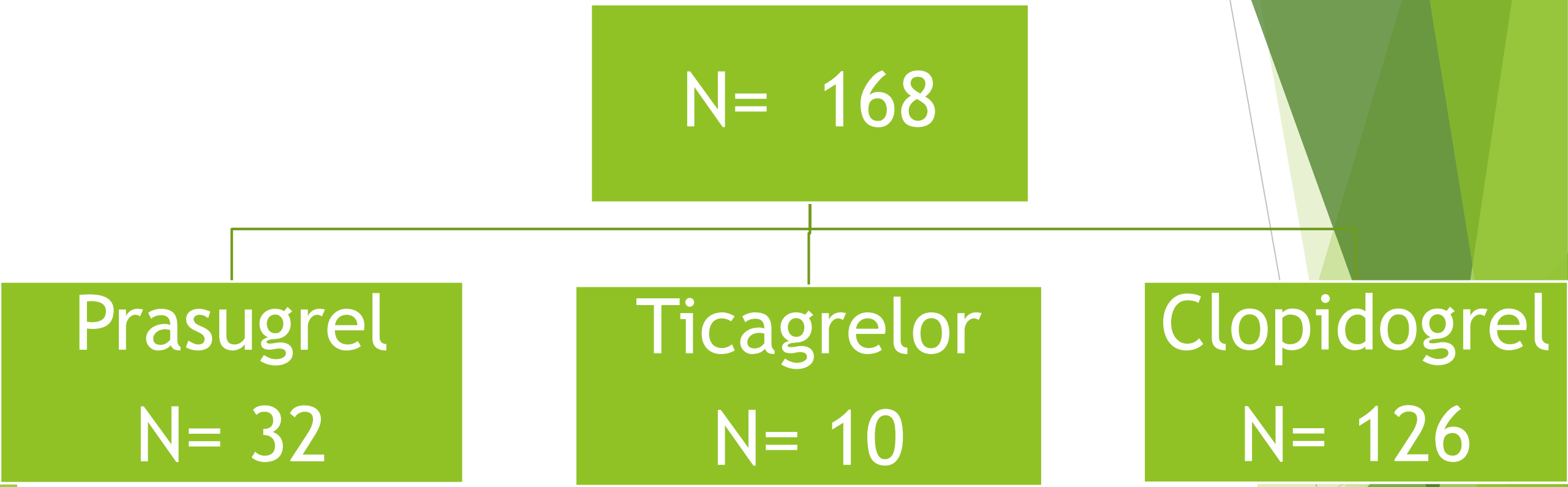
- Six weeks of triple therapy was not superior to 6 months with respect to net clinical outcomes
- Post-hoc landmark analysis from 6 weeks to 9 months: no differences for major bleeding
- Not designed to show non-inferiority

Prasugrel or Ticagrelor

Triple Antithrombotic Therapy with Aspirin, P2Y12 Inhibitor, and Warfarin After Percutaneous Coronary Intervention: An Evaluation of Prasugrel or Ticagrelor Versus Clopidogrel

Verlinden NJ et al. Journal of Cardiovascular Pharmacology and Therapeutics 2017; [Epub ahead of print]

Verlinden et al.



Verlinden et al.

Primary Outcome	Incidence of any bleeding during the 12 month period after index hospitalization
Secondary Outcome	MACCE: cumulative incidence of a composite of cardiac death, nonfatal MI, or nonfatal ischemic stroke within 12 months after index visit

Verlinden et al.

	Ticagrelor or prasugrel (n=42)	Clopidogrel (n=126)	P-value
Any bleeding	12 (28.6%)	16 (12.7%)	0.017 odds ratio: 3.3 (95% CI 1.38-8.34).
MACCE	8 (19%)	23 (18.3%)	0.91
Cardiac death	3 (7.1%)	4 (3.2%)	0.37
MI	7 (16.7%)	20 (15.9%)	0.9
Ischemic stroke	1 (2.4%)	4 (3.2%)	1.0

Verlinden et al.

- The use of prasugrel or ticagrelor as part of triple antithrombotic therapy among patients who underwent PCI and received warfarin was associated with significantly more bleeding compared to patients who received clopidogrel

- Higher potency P2Y12 Inhibitors should be used cautiously in these patients

Verlinden et al.

- Small study population
- Major/minor bleeding not specified
- Adherence and duration of DAPT unknown
- INR values and time in therapeutic range during follow up unknown

Triple Therapy with Aspirin, Prasugrel, and Vitamin K Antagonists in Patients with Drug-Eluting Stent Implantation and an Indication for Oral Anticoagulation

Sarafoff et al. JACC 2013; 61(20): 2060-2066.

Sarafoff et al.

DES placement and 6 months TT

N= 377

Triple Therapy with clopidogrel

N= 256

Triple Therapy with prasugrel

N= 21

Sarafoff et al.

- Prasugrel used if:
- Patients had high platelet reactivity and deemed at increased risk of stent thrombosis (comorbidities, complexity of intervention)
- ACS and already gotten 60 mg prasugrel load
- Patients with clopidogrel allergy
- Patients with previous stent thrombosis while receiving treatment with clopidogrel

Sarafoff et al.

- Assessment of platelet function
- High platelet reactivity to clopidogrel treatment set at 468 arbitrary aggregation units (AU) x min
- Majority patients given 600 mg clopidogrel load, then platelet reactivity tested
- If levels tested and $\geq$ 468 AU x min, then re-loaded with clopidogrel
- If levels still $\geq$ 468 after the 2nd clopidogrel load, then patient got 60 mg prasugrel load

Sarafoff et al.

Primary Outcome	Composite of TIMI major and minor bleeding at 6 months
Secondary Outcome	Composite of death, MI, ischemic stroke, or definite stent thrombosis

Sarafoff et al.

	Prasugrel	Clopidogrel	Hazard Ratio and P-Value
TIMI Bleeding	6 (28.6%)	24 (6.7%)	4.6 (95% CI 1.9-11.4) P < 0.001
MACCE	2 (9.5%)	25 (7.0%)	1.4 (95% CI 0.3-6.1) P 0.61

Sarafoff et al.

- Prasugrel is able to overcome high platelet reactivity to clopidogrel in patients treated with OAC after DES implantation
- Substitution of prasugrel for clopidogrel in patients needing TT increases risk of bleeding
- Lower INR goals used in this trial
  - 2.5-3.0 in patients with mechanical valves
  - 2.0-2.5 for other indications

TRANSLATE-ACS

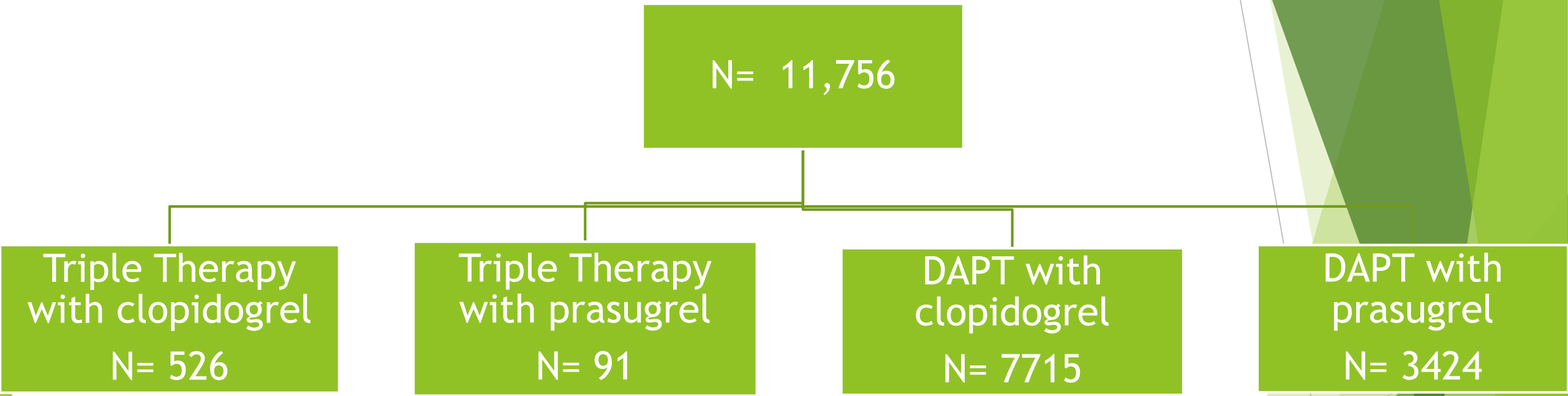
- Comparison of clopidogrel versus prasugrel in nearly 12,000 ACS patients undergoing PCI
- Observational study enrolled STEMI and NSTEMI patients from 2010-2012
- Evaluate “real world” effectiveness and use of prasugrel among MI patients

TRANSLATE-ACS Subanalysis

- Describes prevalence of triple therapy use
- Compares clinical characteristics and outcomes between patients receiving TT and DAPT
- Compares clinical characteristics and outcomes between patients receiving TT with clopidogrel versus prasugrel

Jackson et al. JACC: Cardiovascular Interventions 2015; 8(14): 1880-1889

TRANSLATE-ACS Subanalysis



TRANSLATE-ACS Subanalysis

- TT associated with greater risk of bleeding than DAPT, regardless of which P2Y12 inhibitor used
- No significant difference in composite risk of MACE between groups
- Among those patients discharged on TT, prasugrel associated with higher risk of bleeding than clopidogrel
  - Driven by patient reported events
  - No significant difference in risk of bleeding requiring re-hospitalization between the two groups

Novel Anticoagulants

Rivaroxaban

- 2009: ATLAS ACS-TIMI 46
  - Rivaroxaban in Combination with Aspirin Alone or with Aspirin and a Thienopyridine in Patients with Acute Coronary Syndrome
  - Dose escalation study: placebo, rivaroxaban 5-20 mg total given once daily, and rivaroxaban 5-20 mg total given twice daily
  - Bleed risk increased in a dose-dependent manner
  - Reduction in risk of death, MI, stroke, or severe recurrent ischemia

- 2012: ATLAS ACS 2-TIMI 51
  - Rivaroxaban in Patients with Recent Acute Coronary Syndrome
  - Phase 3 Trial: Placebo vs 2.5 mg twice daily vs 5 mg twice daily
  - Increased risk of bleeding (fewer fatal bleeds with 2.5 mg twice daily dose)
  - Significant reduction in composite of death from CV causes, MI, or stroke

Mega JL et al. Lancet 2009; 374: 29-38.
Mega JL et al. N Engl J Med 2012; 366: 9-

Rivaroxaban

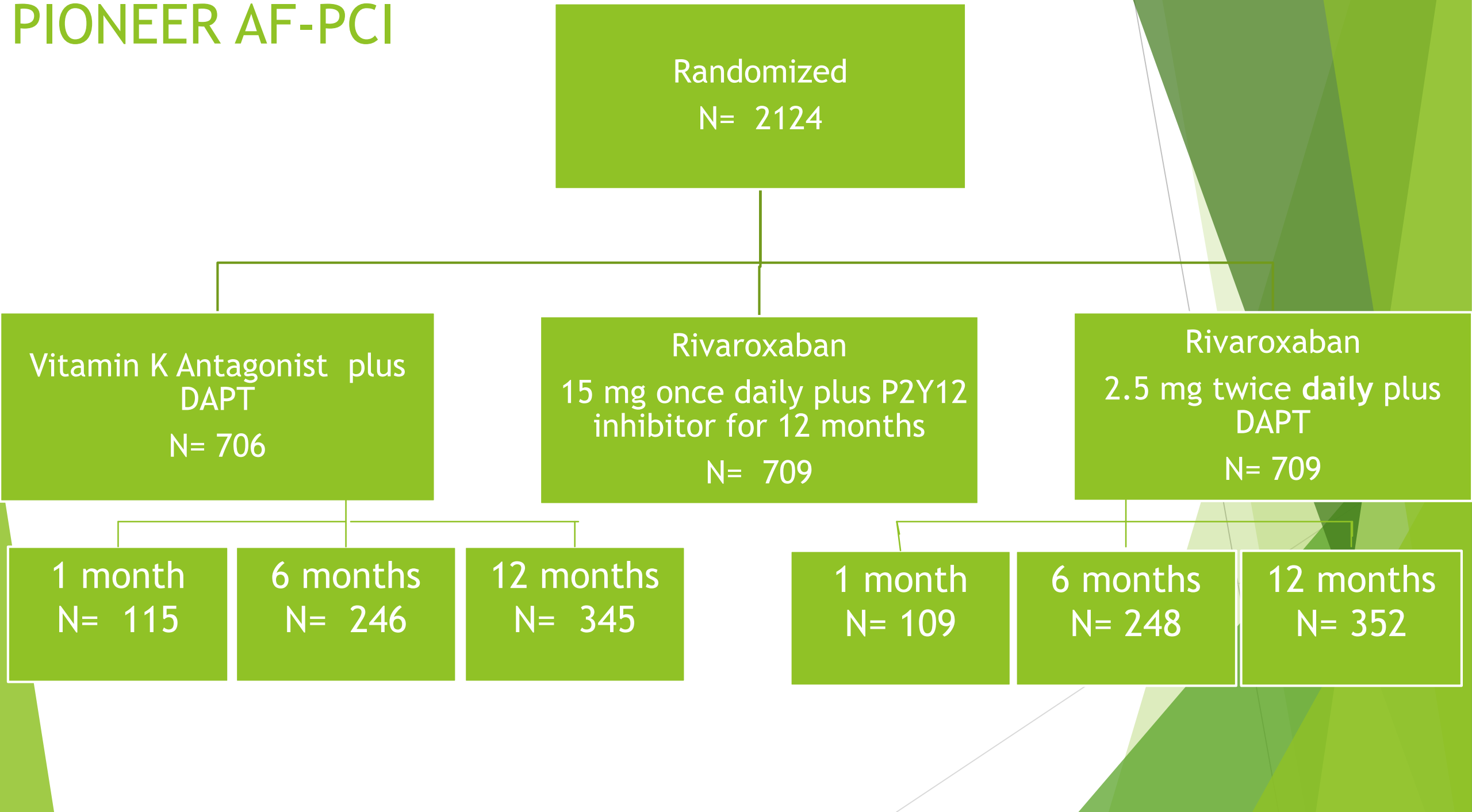
- 2013: European Medicines Agency (EMA) approved rivaroxaban 2.5 mg twice daily for secondary prevention after ACS in combination with DAPT
- 2014: Food and Drug Administration (FDA) rejects approval for expanded indication
- 2015: National Institute for Health and Care Excellence (NICE) in United Kingdom approves use

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

Gibson CM et al. N Engl J Med 2016; 375: 2423-2434.

PIONEER AF-PCI

PIONEER AF-PCI



PIONEER AF-PCI

Inclusion

- 18 years of age or older
- Paroxysmal, persistent, or permanent nonvalvular atrial fibrillation
- Undergone PCI with stent placement

Exclusion

- Any condition that contraindicates anticoagulant therapy:
  - Active bleeding,
  - Hgb < 10 g/dL or platelet count < 90,000 mm^3
  - History of ICH
  - Clinically significant GI bleed within 12 months before randomization
  - Any other condition known to increase risk of bleeding
- History of stroke or TIA
- Cardiogenic shock at time of randomization
- CrCL < 30 ml/min
- Significant liver disease

PIONEER AF-PCI

	Rivaroxaban 15 mg once daily plus P2Y12 inhibitor (Group 1)	Rivaroxaban 2.5 mg twice daily plus DAPT (Group 2)	Vitamin K Antagonist plus DAPT (Group 3)	Hazard Ratio and P-Value
Clinically significant bleeding= composite of major bleeding or minor bleeding (TIMI) at 12 months	16.8%	18%	26.7%	Group 1 vs Group 3: 0.59 (95% CI 0.47-0.76) P < 0.001 Group 2 vs Group 3: 0.63 (95% CI 0.5-0.8) P < 0.001
Major adverse CV event composite of death from CV causes, MI, or stroke)	6.5%	5.6%	6.0%	P > 0.05 for both comparisons

PIONEER AF-PCI

- Treatment that included either low dose or very-low-dose rivaroxaban was associated with a lower risk of clinically significant bleeding than was standard triple therapy that included a VKA

- Rates of major adverse CV events were similar
  - Broad confidence intervals diminish surety of any conclusions regarding efficacy

Table 3. Cumulative Incidence of Secondary Efficacy End Points, with Stratification According to Intended Duration of DAPT.[a]

Cohort and End Point	Group 1	Group 2	Group 3	Group 1 vs. Group 3		Group 2 vs. Group 3	
	No. of Participants with Events (Kaplan–Meier Event Rate)			Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants — no.	694	704	695				
Major adverse cardiovascular event	41 (6.5)	36 (5.6)	36 (6.0)	1.08 (0.69–1.68)	0.75	0.93 (0.59–1.48)	0.76
Death from cardiovascular causes	15 (2.4)	14 (2.2)	11 (1.9)	1.29 (0.59–2.80)	0.52	1.19 (0.54–2.62)	0.66
Myocardial infarction	19 (3.0)	17 (2.7)	21 (3.5)	0.86 (0.46–1.59)	0.62	0.75 (0.40–1.42)	0.37
Stroke	8 (1.3)	10 (1.5)	7 (1.2)	1.07 (0.39–2.96)	0.89	1.36 (0.52–3.58)	0.53
Stent thrombosis	5 (0.8)	6 (0.9)	4 (0.7)	1.20 (0.32–4.45)	0.79	1.44 (0.40–5.09)	0.57
Major adverse cardiovascular event or stent thrombosis	41 (6.5)	36 (5.6)	36 (6.0)	1.08 (0.69–1.68)	0.75	0.93 (0.59–1.48)	0.76
Participants assigned to DAPT for 1 mo — no.		108	112				
Major adverse cardiovascular event		6 (5.8)	5 (5.2)			1.17 (0.36–3.84)	0.79
Death from cardiovascular causes		2 (2.1)	2 (2.2)			0.96 (0.13–6.80)	0.97
Myocardial infarction		3 (2.9)	1 (1.1)			2.93 (0.30–28.16)	0.33
Stroke		2 (1.9)	3 (3.1)			0.65 (0.11–3.91)	0.64
Stent thrombosis		2 (1.9)	1 (1.1)			1.97 (0.18–21.74)	0.57
Major adverse cardiovascular event or stent thrombosis		6 (5.9)	5 (5.2)			1.17 (0.36–3.84)	0.79
Participants assigned to DAPT for 6 mo — no.		248	243				
Major adverse cardiovascular event		16 (7.0)	9 (4.3)			1.72 (0.76–3.88)	0.19
Death from cardiovascular causes		6 (2.8)	4 (1.9)			1.45 (0.41–5.12)	0.57
Myocardial infarction		7 (3.0)	6 (2.9)			1.13 (0.38–3.37)	0.82
Stroke		6 (2.7)	0				0.02
Stent thrombosis		4 (1.7)	1 (0.4)			3.91 (0.44–35.02)	0.19
Major adverse cardiovascular event or stent thrombosis		16 (7.0)	9 (4.3)			1.72 (0.76–3.40)	0.19
Participants assigned to DAPT for 12 mo — no.		348	340				
Major adverse cardiovascular event		14 (4.5)	22 (7.4)			0.57 (0.29–1.11)	0.10
Death from cardiovascular causes		6 (1.9)	5 (1.7)			1.08 (0.33–3.55)	0.89
Myocardial infarction		7 (2.3)	14 (4.8)			0.44 (0.18–1.10)	0.07
Stroke		2 (0.6)	4 (1.3)			0.46 (0.08–2.51)	0.36
Stent thrombosis		0	2 (0.8)				0.10
Major adverse cardiovascular event or stent thrombosis		14 (4.5)	22 (7.4)			0.57 (0.29–1.11)	0.10

PIONEER AF-PCI

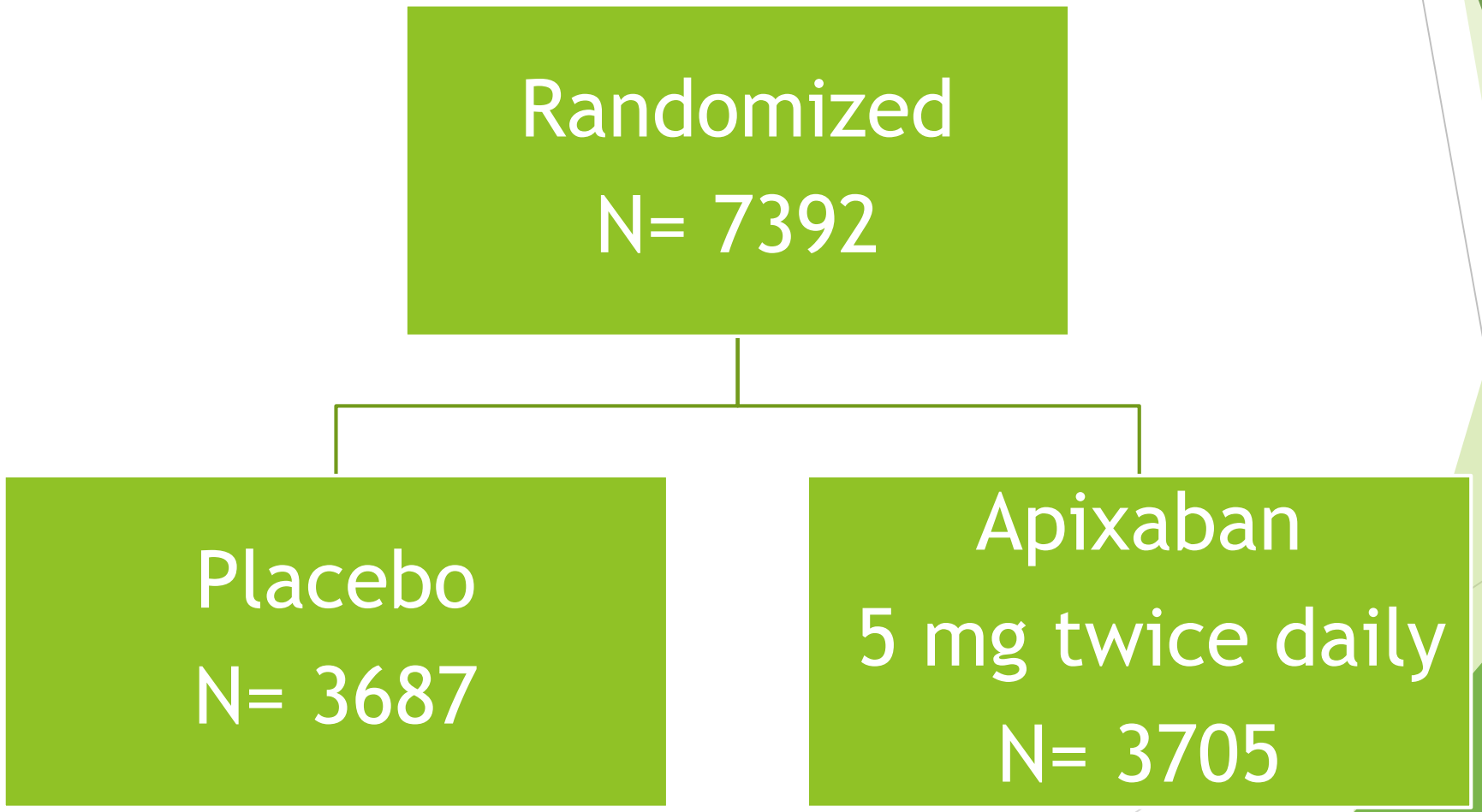
- Trial not powered to establish superiority or non-inferiority
- Individual efficacy endpoints within subgroups are underpowered

Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome

Alexander JH et al. N Engl J Med 2011; 365: 699-708

APPRAISE-2

APPRAISE-2


Randomized
N= 7392
Placebo
N= 3687
Apixaban
5 mg twice daily
N= 3705

APPRAISE-2

Inclusion

- ACS within last 7 days
- at least two or more high-risk characteristics:
  - age 65 years or above
  - diabetes mellitus
  - MI within the previous 5 years
  - Cerebrovascular disease
  - Clinical heart failure requiring or left ventricular ejection fraction < 40% associated with index event
  - peripheral vascular disease,
  - Impaired renal function CrCl < 60 mL/min]
  - no revascularization after the index event

Exclusion

- Persistent severe hypertension
- Severe renal dysfunction with CrCl < 20 ml/min
- Active bleeding or high risk for bleeding
- Known coagulopathy
- Ischemic stroke within 7 days
- NYHA class IV heart failure
- Any history of intracranial bleeding
- Hgb < 9 g/dL or platelet count < 100,000 mm^3
- Required ongoing treatment with a parenteral or oral anticoagulant
- Required treatment with high dose aspirin >325 mg daily or strong inhibitor of CYP 3A4
- Severe comorbid condition with life expectancy < 6 months
- Acute pericarditis

APPRAISE-2

Efficacy Outcome

Primary	Composite of CV death, MI, or ischemic stroke
Secondary	• Composite of CV death, MI, ischemic stroke, or unstable angina • Individual components of primary efficacy outcome, unstable angina, and stent thrombosis

Safety Outcome

Primary	Major bleeding (TIMI)
Secondary	• TIMI major and minor bleeding, major or clinically relevant non-major bleeding (ISTH) • Severe or moderate bleeding (GUSTO)

APPRAISE-2

- After ~7000 patients had been recruited, the independent data monitoring committee recommended that the trial be stopped

- “Excess of clinically important bleeding events with apixaban in the absence of a counterbalancing reduction of ischemic events”

APPRAISE-2

	Placebo	Apixaban 5 mg twice daily	Hazard Ratio with Apixaban (95% CI) and P value
TIMI Major Bleeding	18 (0.5%)	46 (1.3%)	2.59 (1.5-4.46) P value 0.001
TIMI Major or Minor Bleeding	29 (0.8%)	80 (2.2%)	2.79 (1.87-3.72) P value < 0.001
Efficacy: Composite of CV death, MI, or ischemic stroke	293 (7.9%)	279 (7.5%)	0.95 (0.8-1.11) P value 0.51

APPRAISE-2

- Treatment with apixaban (as compared with placebo), was associated with a significant increase in risk of bleeding without a significant effect on the incidence of recurrent ischemic events

- Majority of patients (81%) were receiving DAPT at the time of randomization*

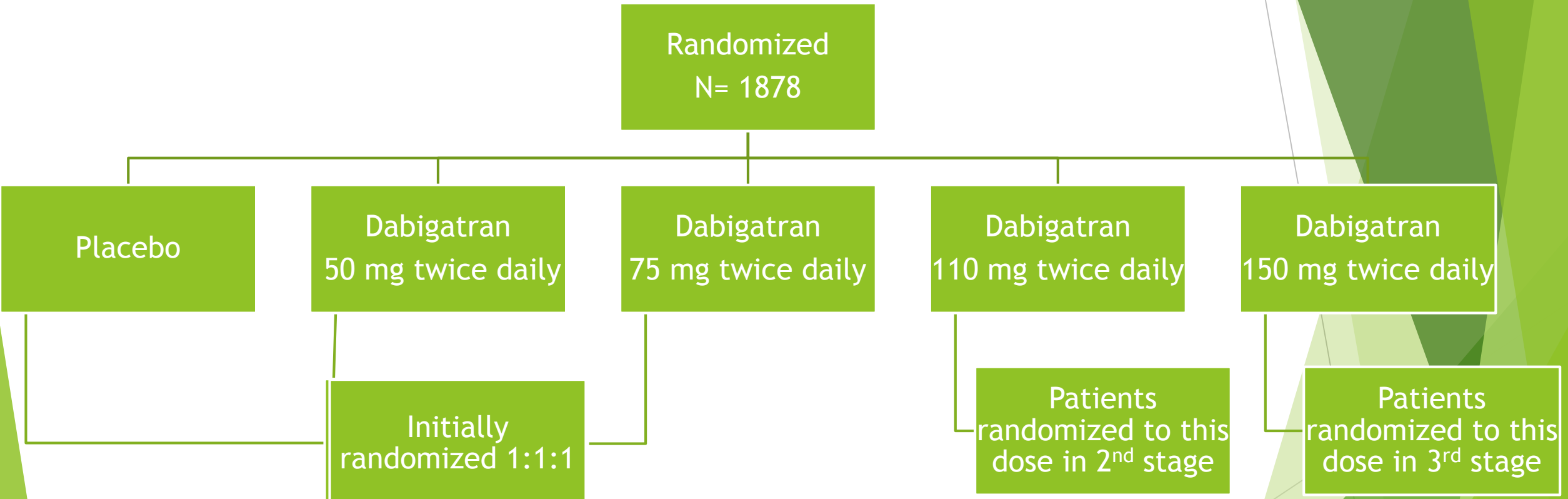
- Trial population had high-risk characteristics
  - More than half-the patients had 3 or more “high-risk” characteristics defined at time of enrollment

Dabigatran vs placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial

Oldgren J et al. European Heart Journal 2011;32: 2781-2789

RE-DEEM

RE-DEEM


Randomized
N= 1878
Placebo
Dabigatran
50 mg twice daily
Dabigatran
75 mg twice daily
Dabigatran
110 mg twice daily
Dabigatran
150 mg twice daily
Initially
randomized 1:1:1
Patients
randomized to this
dose in 2nd stage
Patients
randomized to this
dose in 3rd stage

RE-DEEM

4th stage	Placebo	50 mg twice daily	75 mg twice daily	110 mg twice daily	150 mg twice daily
N	373	372	371	411	351

RE-DEEM

Inclusion

- 18 years or older
- Hospitalized with MI within last 14 days
- Receiving DAPT*
- at least one risk factor for subsequent cardiovascular complications:
  - age 65 years or above
  - diabetes mellitus on treatment,
  - previous MI
  - left bundle branch block,
  - congestive heart failure requiring treatment or left ventricular ejection fraction ,40%,
  - peripheral arterial disease,
  - moderate renal insufficiency [creatinine clearance (CrCl) ≥30 – 60 mL/min]
  - no revascularization for the index event

Exclusion

- Ongoing or planned treatment with VKA
- Severe disabling stroke within the previous 6 months or any stroke within the previous 14 days
- Conditions associated with an increased risk of bleeding:
  - major surgery (including bypass surgery) in the previous month,
  - history of severe bleeding
  - gastrointestinal hemorrhage within the past year
  - gastroduodenal ulcer in the previous 30 days
  - fibrinolytic agents within 48 h of study entry
  - uncontrolled hypertension
  - Hgb < 10 g/dL or platelet count < 100 x 10^9 L
  - Normal coronary arteries at angiogram for index event
  - Congestive heart failure NYHA Class IV
  - Severe renal impairment (CrCl <30 ml/min)

RE-DEEM

Primary outcome

Incidence of major or clinically relevant minor bleeding

Major bleeding events were assessed by:

- ISTH definition
- fall in Hgb of 2 g/dL or more
- transfusion of two units or more of whole blood or packed red blood cells

Clinically relevant minor bleeding was defined as a clinically overt bleed that did not meet criteria for major bleed

Secondary outcome

Indicators of efficacy

Reduction in incidences of CV ischemic events:

- Composite of CV death, non-fatal MI, and non-hemorrhagic stroke
- Individual occurrence of death (CV and all-cause), non-fatal MI, severe recurrent ischemia, and non-hemorrhagic stroke
- Reduction in D-dimer levels

RE-DEEM

	Placebo	Dabigatran 50 mg twice daily	Dabigatran 75 mg twice daily	Dabigatran 110 mg twice daily	Dabigatran 150 mg twice daily
Primary Outcome (%)	2.2	3.5	4.3	7.9	7.8
Hazard Ratio		1.77 95% CI (0.7-4.5)	2.17 95% CI (0.88-5.31)	3.92 95% CI (1.72-8.95)	4.27 95% CI (1.86-9.81)

RE-DEEM

	Placebo	Dabigatran 50 mg twice daily	Dabigatran 75 mg twice daily	Dabigatran 110 mg twice daily	Dabigatran 150 mg twice daily
Secondary Outcome (%)	3.8	4.6	4.9	3.0	3.5

RE-DEEM

- The addition of dabigatran to DAPT for 6 months in post-MI patients was associated with increased risk of bleeding
- The total number of patients experiencing ischemic CV events during the study was low, with minor differences between the treatment groups

Upcoming Studies

AUGUSTUS

Apixaban 5 mg twice daily + P2Y12 inhibitor + aspirin or placebo

Vs

Warfarin + P2Y12 inhibitor + aspirin or placebo

- N= 4600
- Primary outcome: major/clinically relevant bleeding (6 months)
- Secondary objective: death, MI, stroke, stent thrombosis
- Estimated study completion date: December 2018

REDUAL-PCI

110 mg dabigatran twice daily + clopidogrel or ticagrelor

vs

150 mg dabigatran BID + clodpidogrel or ticagrelor

vs

Triple therapy: warfarin + clopidogrel or ticagrelor + aspirin

- Study aims to show non-inferiority of each dose of dual antithrombotic therapy when compared to triple antithrombotic therapy
- Safety endpoint= time to first major bleeding event (30 month)
- Efficacy endpoint= composite of time to death or first thrombotic event (all death, MI, stroke, or systemic embolism) and unplanned revascularization
- N= 2727
- Estimated completion date: final data collection June 2017 (results end of year)

Summary	
WOEST	Triple therapy for 1 year increased risk of bleeding
ISAR-TRIPLE	Six weeks of triple therapy was not superior to 6 months with respect to net clinical outcomes
Verlinden et al.	Prasugrel or ticagrelor as part of TT was associated with significantly more bleeding compared to patients who received clopidogrel
Sarafoff et al.	Substitution of prasugrel for clopidogrel in patients needing TT increases risk of bleeding
Translate-ACS	Prasugrel has higher risk of bleeding in TT than clopidogrel
PIONEER AF-PCI	Low dose or very-low-dose rivaroxaban was associated with a lower risk of clinically significant bleeding than was standard triple therapy that included a VKA
APPRAISE-2	Apixaban (as compared with placebo), was associated with a significant increase in risk of bleeding without a significant effect on the incidence of recurrent ischemic events
RE-DEEM	The addition of dabigatran to DAPT for 6 months in post-MI patients was associated with increased risk of bleeding

Conclusions

- Assess each patient for risk of bleeding and risk of ischemic events
- TT for as short of duration as possible
- Clopidogrel preferred P2Y12 inhibitor
- Newer oral anticoagulants have higher risk of bleeding
  - Low dose rivaroxaban and DAPT had lower risk of bleeding than warfarin and DAPT