Triple Antithrombotic Therapy after PCI- Warfarin vs. DOACs

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Disclosure

- No financial or conflict of interest to disclose

Objectives

1. Discuss clinically relevant trials regarding anticoagulant therapy after percutaneous coronary intervention (PCI)
2. Describe the difference between double vs. triple antithrombotic therapy
3. Analyze bleeding rates for patients on different triple antithrombotic therapy regimens post PCI

PCI & AF

- The majority of patients with atrial fibrillation (AF) require oral anticoagulation (OAC) to decrease risk of stroke
- Patients who undergo percutaneous coronary intervention (PCI) require dual antiplatelet therapy (DAPT) to reduce risk of ischemic complications
- Approximately 5-10% of patients undergoing PCI have AF
- Triple antithrombotic therapy increases the risk of bleeding

Capodanno D. J Am Coll Cardiol 2019; 74:83-99.

Guideline Recommendations

- Choice of oral anticoagulant is at the discretion of the provider and patient (COR I, LOE C)
- Choice of anticoagulant:
  - DOAC preferred over warfarin (COR I, LOE A)
- Choice of P2Y12 inhibitor: Clopidogrel (COR IIa, LOE B)
  - Ticagrelor may be a reasonable option
  - Avoid prasugrel- ↑ bleeding

Capodanno D. J Am Coll Cardiol 2019; 74:83-99.
Angiolillo S.G. Circulation 2018;138:527-536.
January C.T. Circulation 2019; 140:e125-e151.

Double vs. Triple Therapy

- Double (OAC plus P2Y12 inhibitor) preferred in most patients
- Triple (OAC plus P2Y12 inhibitor plus ASA) consider for high thrombotic risk

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Previous Trials

Trial	End points	Treatment Arms			Results
RE-Dual PCI Trial		Warfarin + ASA + P2Y12 inhibitor; N=981	Dabigatran 110mg BID + P2Y12 inhibitor; N=981	Dabigatran 150mg BID + P2Y12 inhibitor; N=736	Dabigatran vs. Warfarin
	Safety: ISTH major or CRNMB	26.9%	15.4%	20.2%	P<0.001 D110 P=0.002 D150
	Efficacy: Death, MI, stroke, systemic embolism, or unplanned revascularization	13.4%	15.2%	11.8%	P=0.30 D110 P=0.44 D150
PIONEER AF-PCI Trial		Warfarin + ASA + P2Y12 inhibitor; N=706	Rivaroxaban 2.5mg BID + ASA+ P2Y12 inhibitor; N=709	Rivaroxaban 15mg daily + P2Y12 inhibitor; N=709	Rivaroxaban vs. Warfarin
	Safety: TIMI criteria for major and minor bleeding	26.7%	18%	16.8%	P<0.001 R2.5 P<0.001 R15
	Efficacy: CV death, MI, stroke	6%	5.6%	6.5%	P=0.75 R15 P= 0.76 R2.5
AUGUSTUS Trial		Warfarin + P2Y12 + ASA; N=1123	Apixaban + P2Y12 inhibitor + Placebo; N=1143	Apixaban + P2Y12 inhibitor + ASA; N=1145	Apixaban vs. Warfarin
	Safety: ISTH major or CRNMB	18.7%	7.3%	13.8%	P<0.001
	Death or Hospitalization	27.5%	22%	24.9%	P=0.002
	Death or ischemic event	5.7%	6.2%	6.2%	

Cannon C.P. N Engl J Med 2017; 377:1513-24.
Gibson M.C. N Engl J Med 2016; 375:2423-34.
Lopes R.D. N Engl J Med 2019; 380:1509-24.

Remaining Questions/Issues

- Further research needed to compare triple therapy with warfarin vs. DOACs
- Purpose:
  - To determine if there is a difference in the incidence of bleeding for patients with AF receiving triple therapy post PCI with DOACs plus DAPT vs. warfarin plus DAPT
- Goal is to help guide clinicians to the most appropriate triple therapy combination for our patient population

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Hypothesis

- In patients with AF undergoing PCI with stent placement, DOACs plus DAPT (ASA + P2Y12 inhibitor) will have less bleeding and be noninferior for thrombosis compared to warfarin plus DAPT

Design

- Retrospective, cohort study
  - July 1, 2014 to October 31, 2019
  - Bleeding incidence (cardiology follow up visit 4 +/- 2 weeks)
  - Secondary cardiovascular endpoints (+/- 6 months)
- Comparative groups:
  - DOAC + ASA + P2Y12 inhibitor
  - Warfarin + ASA + P2Y12 inhibitor
  - Clopidogrel + ASA + OAC
  - Ticagrelor or prasugrel + ASA + OAC

Outcomes

- Primary: Bleeding
- Secondary:
  - Thromboembolic events
  - Pharmacist intervention
  - Hospital readmission

Study Population

- Inclusion Criteria:
  - All patients ≥ 18 years who have AF and PCI with stent placement during the admission
    - Treatment with OAC (warfarin, apixaban, rivaroxaban, dabigatran, or edoxaban) and DAPT (ASA + P2Y12 inhibitor) at discharge
- Exclusion Criteria:
  - Lack of follow up visit after 6 weeks
  - Women who are pregnant or breastfeeding

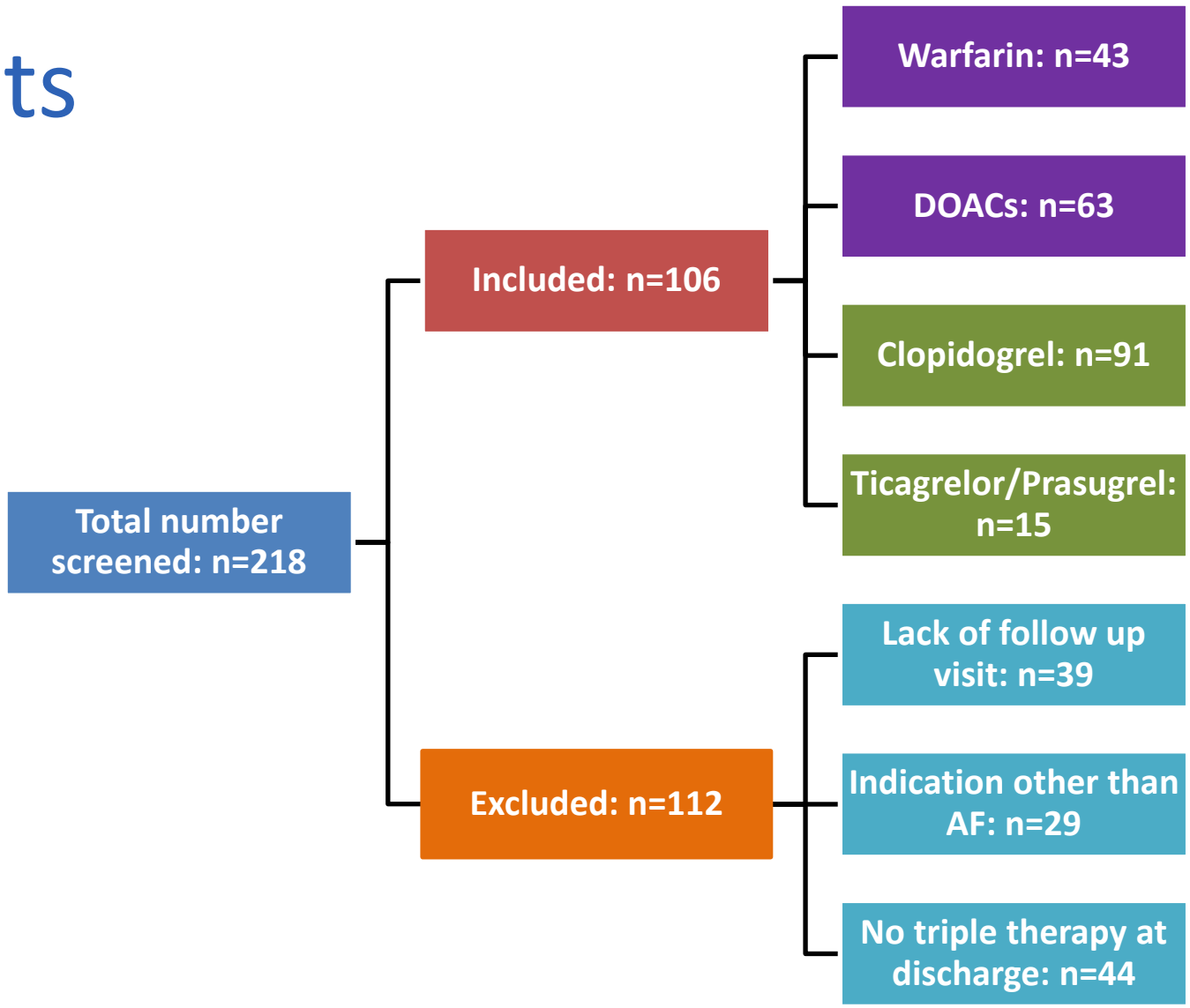
Statistical Analysis

- Sample Size: 868 patients (434 each arm)
  - Estimated incidence of 10% vs. 5% to obtain 80% power
- Alpha <0.05
- Discrete data: Chi Squared test and Fisher's exact
- Continuous data: Unpaired T-test

Subgroup Analysis

- P2Y12 inhibitor and associated type of bleed
- DOAC and associated type of bleed
- Clopidogrel vs. ticagrelor/prasugrel bleeding risk
- INR target
- CrCl <30ml/min

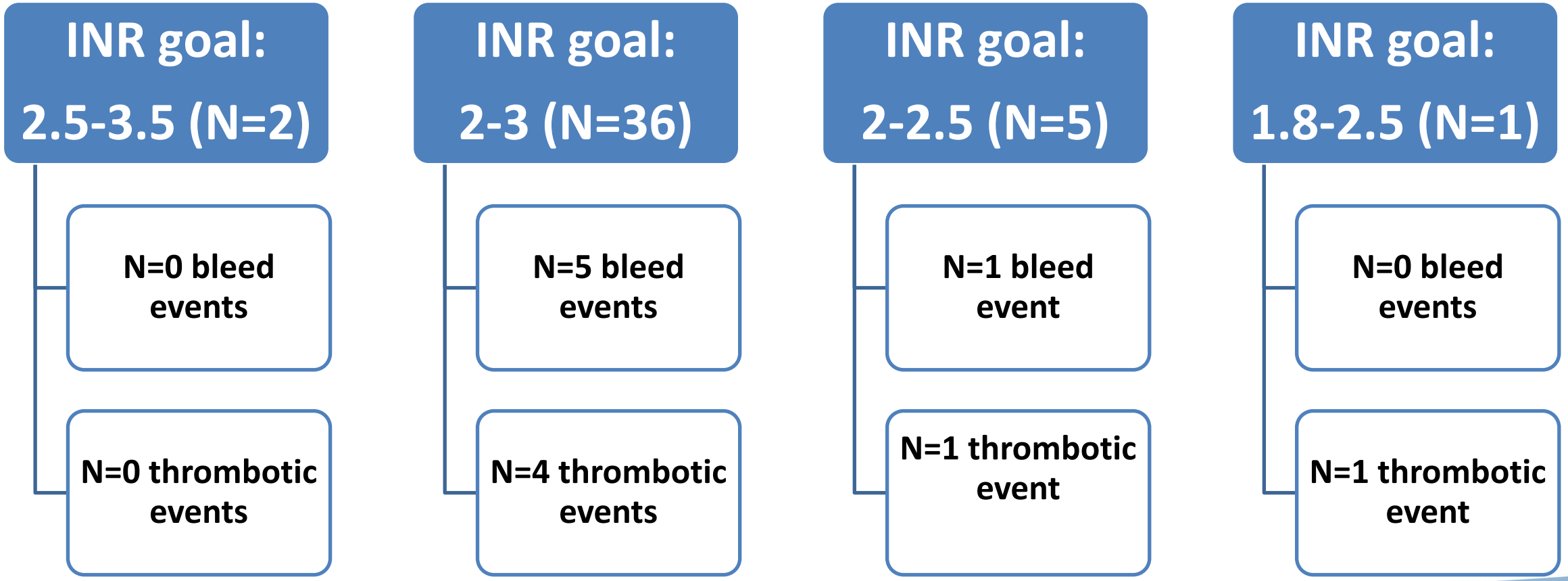
Patients



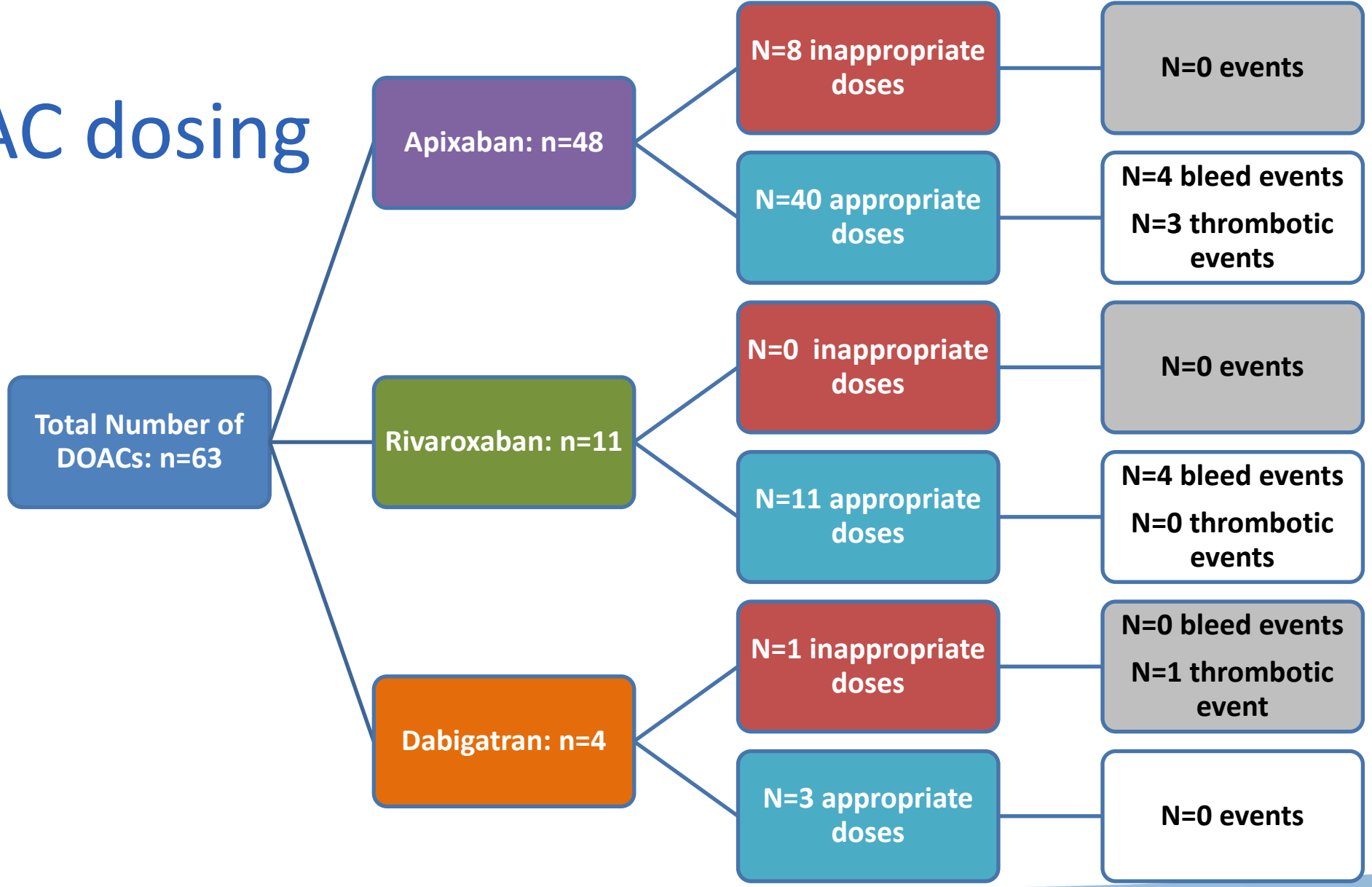
OAC Baseline Characteristics

Characteristic	Warfarin (n= 43)	DOACs (n= 63)	CI	P value
Age- yrs	77.4	74.4	(6.23-0.51)	0.09
Male- no. (%)	30 (70%)	45 (71%)		0.52
BMI- kg/m2	28.3	30.2	(-4.28-0.48)	0.12
CrCl- ml/min	69.3	86.3	(-30.62- -3.49)	0.01
GI prophylaxis- no. (%)	17 (40%)	36 (57%)		0.11
CHADSVASc Score	4.7	4.0	(0.10-1.36)	0.02
HAS-BLED Score	2.3	2.3	(-0.32-0.26)	0.83
PARIS Thrombosis Score	5.5	4.0	(0.64-2.40)	0.001
PARIS Bleeding Score	7.4	6.4	(0.14-1.79)	0.02

Warfarin INR goal



DOAC dosing



DAPT Baseline Characteristics

Characteristic	Clopidogrel (n= 91)	Ticagrelor/Prasugrel (n= 15)	CI	P value
Age- yrs	75.9	74.3	(3.28-6.44)	0.52
Male- no. (%)	62 (68%)	13 (87%)		0.25
BMI- kg/m2	29.6	28.7	(-2.47-4.31)	0.12
CrCl- ml/min	78.9	82.6	(-23.43-15.90)	0.71
GI prophylaxis- no. (%)	45 (50%)	8 (53%)		0.78
CHADSVASc Score	4.3	3.8	(-0.36-1.44)	0.24
HAS-BLED Score	2.3	2.5	(-0.65-0.16)	0.23
PARIS Thrombosis Score	4.4	6.0	(-2.86- -0.32)	0.01
PARIS Bleeding Score	6.9	6.1	(-0.36-2.01)	0.17

Primary Safety Endpoint

	Warfarin* (n= 43)	DOACs (n=63)	P value
Any bleeding- no. (%)	6 (14%)	8 (13%)	0.85
Major bleed	1	0	
CRNMB	5	8	

*INR was >3 in two patients

Secondary Safety Endpoint

	Clopidogrel (n= 91)	Ticagrelor/Prasugrel (n= 15)	P value
Any bleeding- no. (%)	9 (10%)	5 (33%)	0.04
Major bleed	1	0	
CRNMB	8	5	

Secondary Efficacy Endpoint

	Warfarin* (n= 43)	DOACs (n=63)	P value
Any thrombotic event- no. (%)	5 (12%)	4 (6%)	0.36
Stroke	1	1	
Systemic embolism	1	0	
Unplanned revascularization	3	3	

*INR was <2 in four patients

Secondary Efficacy Endpoint

	Clopidogrel (n= 91)	Ticagrelor/Prasugrel (n= 15)	P value
Any thrombotic event- no. (%)	8 (9%)	1 (7%)	1.00
Stroke	2	0	
Systemic embolism	1	0	
Unplanned revascularization	5	1	

Secondary Endpoints

	Warfarin (n= 43)	DOACs (n=63)	P value
Pharmacy Education- no. (%)	30 (70%)	40 (63%)	0.21
Hospital readmissions- no. (%)	25 (58%)	27 (43%)	0.18
Duration of triple therapy- days	99	85	0.31
Duration of double therapy- days	173	178	0.13

Secondary Endpoints

	Clopidogrel (n= 91)	Ticagrelor /Prasugrel (n= 15)	P value
Pharmacy Education- no. (%)	62 (68%)	8 (53%)	0.41
Hospital readmissions- no. (%)	42 (46%)	10 (67%)	0.23
Duration of triple therapy- days	87	110	0.22
Duration of double therapy- days	176	180	0.34

Conclusions

- There was no significant difference in the incidence of bleeding when comparing warfarin vs. DOACs in triple therapy post PCI
- The use of ticagrelor or prasugrel increased the risk of bleeding compared to clopidogrel

Strengths

- Evaluate relationship between warfarin vs. DOACs
- Triple therapy assessment
- No significant baseline differences
- Clinically relevant endpoints
- Statistical tests were appropriate

Limitations

- Retrospective study
- Limited generalizability
- Inaccurate or incomplete historical data in EMR
- Composite endpoints
- Lack of power

Summary and Recommendation

- Triple therapy in patients with AF undergoing PCI can be associated with increased risk of bleeding
- There was no significant difference in the incidence of bleeding or thrombotic events when comparing warfarin vs. DOACs
- Clopidogrel is associated with less bleeding risk than ticagrelor or prasugrel

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