POPULAR TAVI TRIAL

A Randomized, Open Label, Multicenter Study of Oral Anticoagulation with or without Clopidogrel after Transcatheter Aortic Valve Implantation

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on behalf of the POPULAR TAVI investigators

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Disclosures Dr Nijenhuis

- None.

Background

- TAVI remains associated with frequent complications:
  - Major and life-threatening bleeding: 3-15%
  - Stroke: 1-8%
- Approximately 30% of patients have atrial fibrillation (AF)
- In these patients, the risk of thromboembolic events is higher

1. Mack et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med 2019;380(18):1695–705.
2. Popma et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med 2019;380(18):1706–15.
3. Leon et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2016;374(17):1609–20.
4. Reardon et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2017;376(14):1321–31.
5. Thyregod et al. 1-year results from the all-comers NOTION randomized clinical trial. J Am Coll Cardiol 2015;65(20):2184–94.

Background

- Patients with AF undergoing TAVI are in need of oral anticoagulation (OAC) to reduce stroke and thromboembolism
- Antiplatelet therapy in addition to OAC may decrease thromboembolism after TAVI but increases bleeding

1. Kosmidou et al. Antithrombotic Therapy and Cardiovascular Outcomes After Transcatheter Aortic Valve Replacement in Patients With Atrial Fibrillation. JACC Cardiovasc Interv 2019;12(16):1580–9
2. Abdul-Jawad Altisent et al. Warfarin and Antiplatelet Therapy Versus Warfarin Alone for Treating Patients With Atrial Fibrillation Undergoing Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv 2016;9(16):1706–17.

Background

Guidelines on the management of valvular heart disease (version 2012)

The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Despite the lack of evidence, a combination of low-dose aspirin and a thienopyridine is used early after TAVI and percutaneous edge-to-edge repair, followed by aspirin or a thienopyridine alone. In patients in AF, a combination of vitamin K antagonist and aspirin or thienopyridine is generally used, but should be weighed against increased risk of bleeding.

POPULAR TAVI COHORT A
PATIENTS *WITHOUT* OAC
N=665

POPULAR TAVI COHORT B
PATIENTS *WITH* OAC
N=313

Background

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POPULAR TAVI COHORT B
PATIENTS *WITH* OAC
N=313

Hypothesis

OAC alone vs. *OAC + 3 months clopidogrel*, is:

- Superior for bleeding (primary outcome),
- Non-inferior for the composite of CV death, stroke, MI, non-procedural bleeding (secondary outcome),
- Non-inferior for the composite of CV death, ischemic stroke, MI (secondary outcome).

Trial Organization

- Trial Design
  - Investigator initiated, randomised, open-label, blinded CEC
- Sponsor and coordinating center
  - St. Antonius Hospital, Nieuwegein, The Netherlands
- Funding and Support
  - Dutch Organization for Health Research and Development ZonMw (project no. 836031014)

Recruitment

- Participating Sites (17)
  - Netherlands
  - Belgium
  - Luxembourg
  - Czech Republic

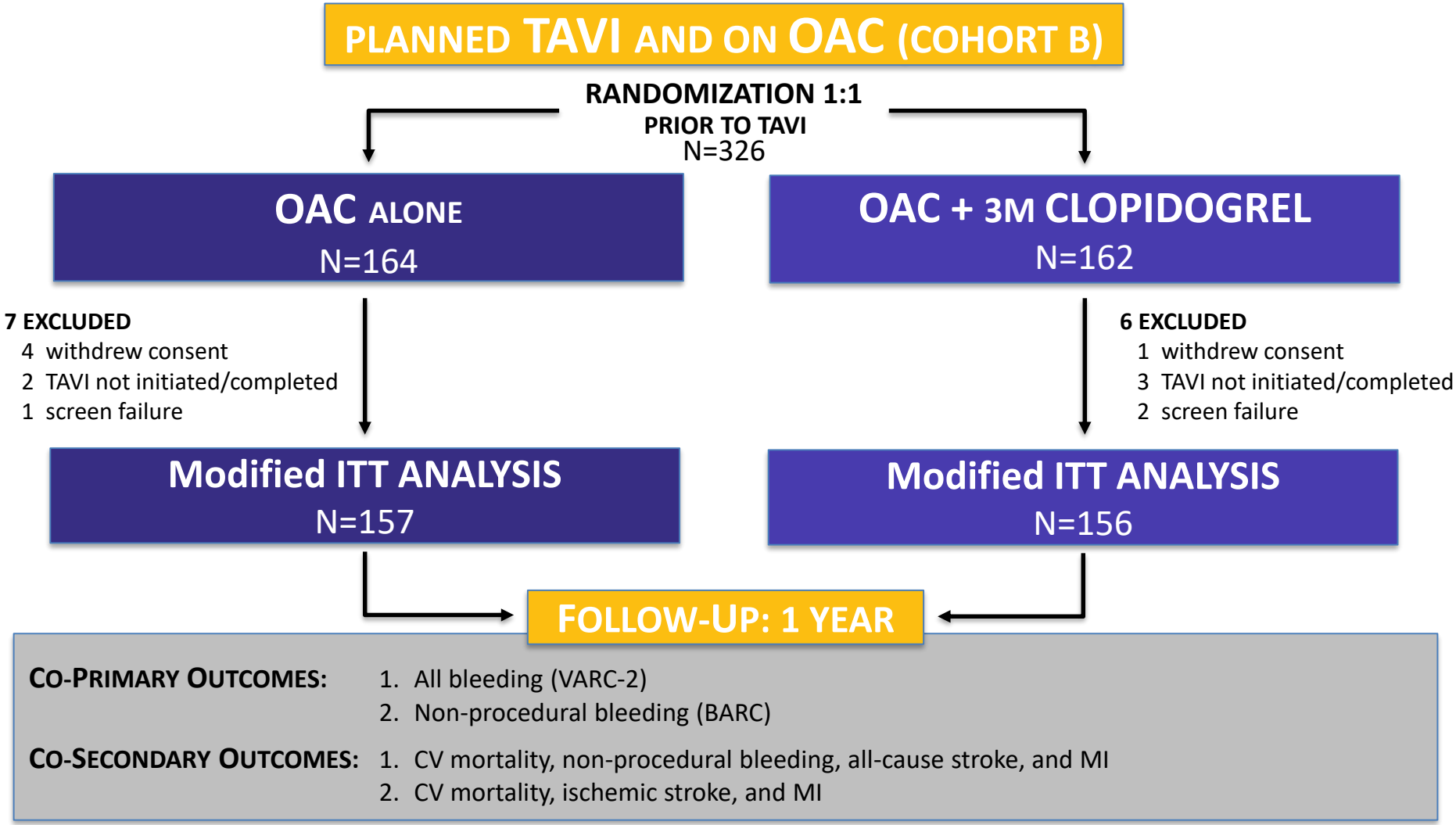
Study Population

Inclusion

- Long-term indication for OAC
- Written informed consent

Exclusion

- DES within 3 months before TAVI
- BMS within 1 month before TAVI
- Allergy or contraindication to OAC or clopidogrel


PLANNED TAVI AND ON OAC (COHORT B)
RANDOMIZATION 1:1
PRIOR TO TAVI
N=326
OAC ALONE
N=164
OAC + 3M CLOPIDOGREL
N=162
7 EXCLUDED
4 withdrew consent
2 TAVI not initiated/completed
1 screen failure
6 EXCLUDED
1 withdrew consent
3 TAVI not initiated/completed
2 screen failure
Modified ITT ANALYSIS
N=157
Modified ITT ANALYSIS
N=156
FOLLOW-UP: 1 YEAR
CO-PRIMARY OUTCOMES:
1. All bleeding (VARC-2)
2. Non-procedural bleeding (BARC)
CO-SECONDARY OUTCOMES:
1. CV mortality, non-procedural bleeding, all-cause stroke, and MI
2. CV mortality, ischemic stroke, and MI

Study Power

- Primary outcomes:
  - Superiority, power 80%, alpha 0.05
  - Expected event rate OAC vs. OAC + clopidogrel: 18% vs. 36%
- Secondary outcomes:
  - Non-inferiority, non-inferiority margin: 7.5%
  - Expected event rate OAC vs. OAC + clopidogrel: 31% vs. 39%

Adherence and Cross-Overs

- Adherence for 3 months clopidogrel: 95.5%
- Duration clopidogrel: median 91 days [IQR 89-92]
- Cross-overs: one in each group

Baseline

	OAC (N=157)	OAC + CLOPIDOGREL (N=156)
Age - yr	81±6	81±6
Female - no. (%)	69 (43.9)	73 (46.8)
NYHA class III or IV – no. (%)	119 (75.8)	110 (70.1)
STS risk score - % [IQR]	3.2 [2.2 - 4.8]	3.1 [2.3 - 4.5]
Atrial fibrillation - no. (%)	150 (95.5)	147 (94.2)
Coronary artery disease - no. (%)	65 (41.4)	69 (44.2)
Peripheral artery disease - no. (%)	30 (19.1)	28 (17.9)
Previous stroke - no. (%)	15 (9.6)	15 (9.6)
Estimated GFR - ml/min/1.73 m^2	53±18	56±17
LVEF – no. (%)		
>50%	91 (58.0)	97 (62.2)
30-50%	54 (34.4)	46 (29.5)
≤30%	12 (7.6)	13 (8.3)

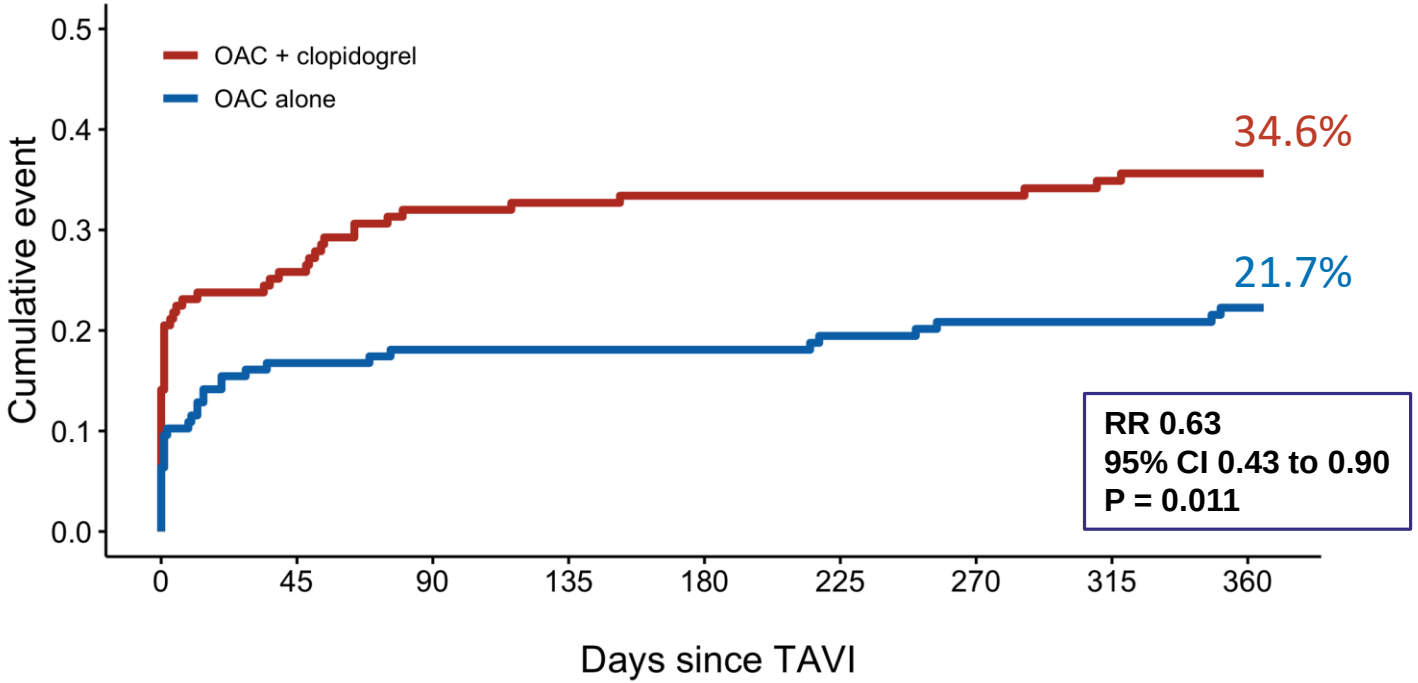
Anticoagulation

	OAC (N=157)	OAC + CLOPIDOGREL (N=156)
Vitamin K antagonist – no. (%)	118 (75.2)	110 (70.5)
Acenocoumarol	97 (61.8)	91 (58.3)
Phenprocoumon	18 (11.5)	16 (10.3)
Warfarin	3 (1.9)	3 (1.9)
Direct oral anticoagulant – no. (%)	37 (23.6)	46 (29.5)
Apixaban	14 (8.9)	25 (16.0)
Dabigatran	7 (4.5)	4 (2.6)
Edoxaban	4 (2.5)	4 (2.6)
Rivaroxaban	12 (7.6)	12 (7.6)
Low molecular weight heparin – no (%)	2 (1.3)	0 (0)

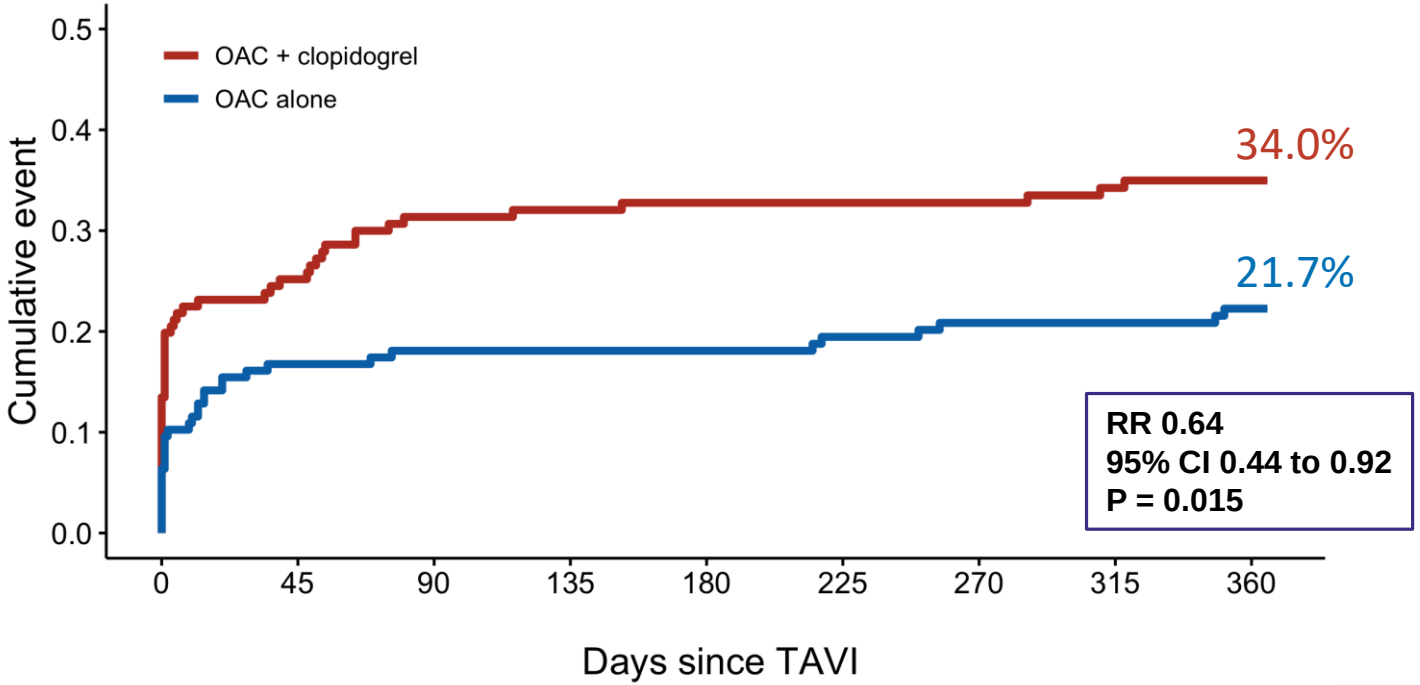
Procedure

	OAC (N=157)	OAC + CLOPIDOGREL (N=156)
Approach		
Transfemoral	136 (86.6)	132 (84.6)
Other	21 (13.4)	24 (15.4)
Unfractionated heparin – no. (%)	157 (100)	156 (100)
Maximal ACT – seconds [IQR]	285 [246-319]	290 [240-330]
Prosthesis – no. (%)		
Sapien 3, Edwards Lifesciences	65 (41.4)	82 (52.6)
CoreValve Evolut R, Medtronic	45 (28.7)	36 (23.1)
Other	47 (29.9)	38 (24.3)
Embolic protection device use – no. (%)	4 (2.5)	6 (3.8)
VARC-2 vascular complication – no (%)	20 (12.7)	35 (22.4)
Minor vascular complication	12 (7.6)	17 (10.9)
Major vascular complication	8 (5.1)	18 (11.5)

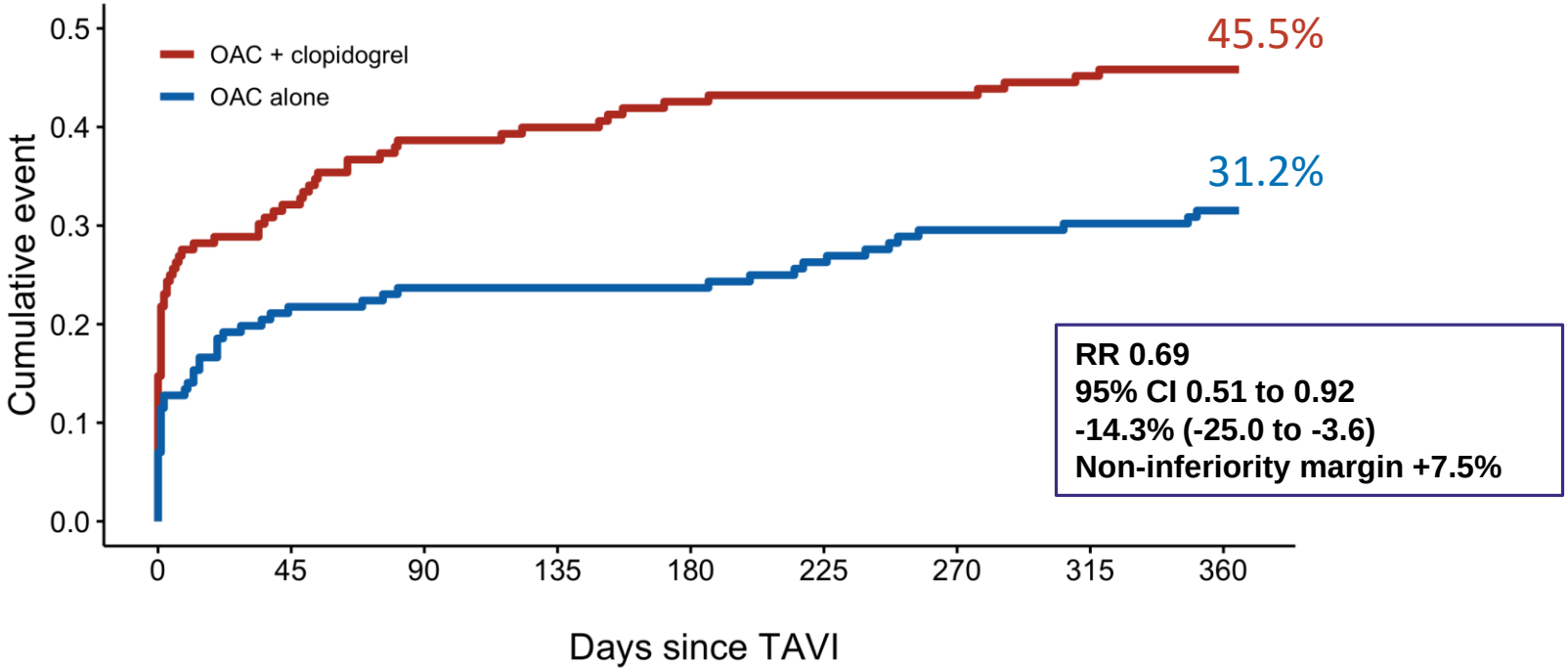
All Bleeding



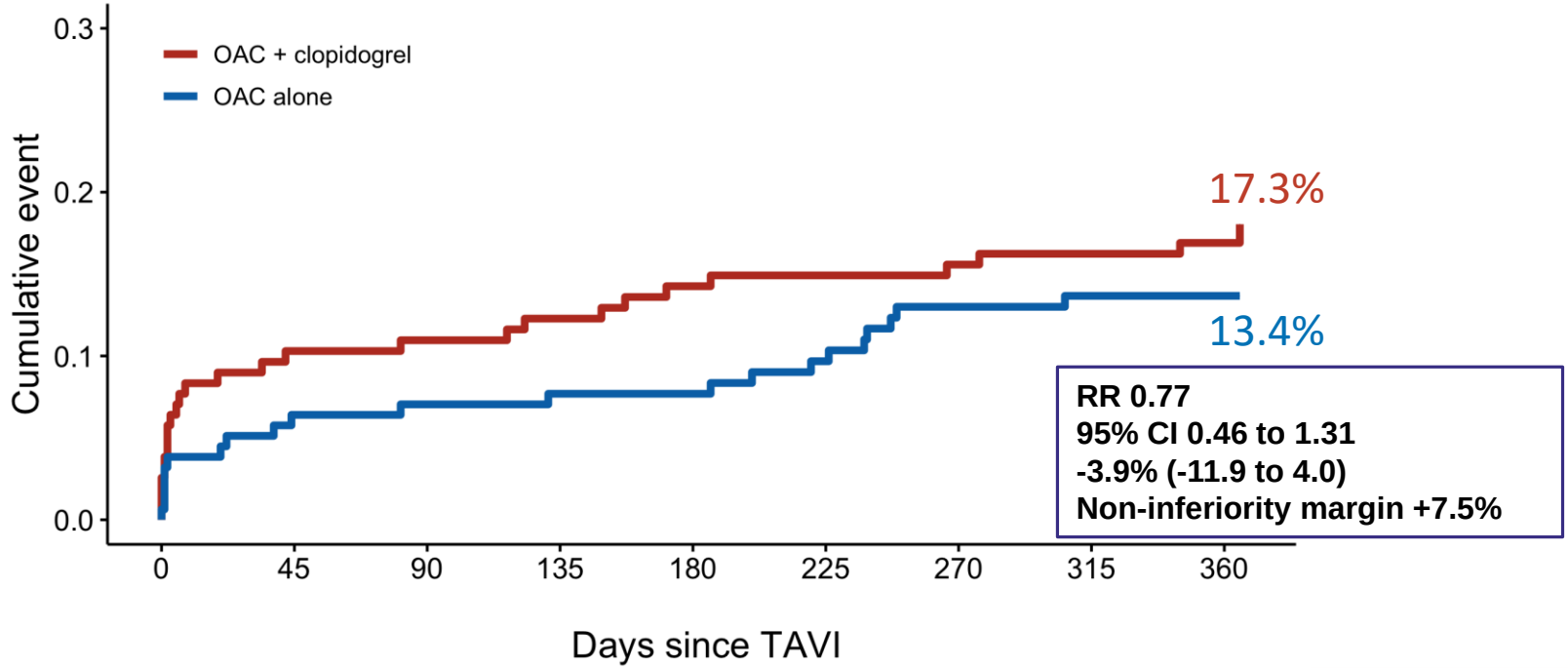
Non-Procedural Bleeding



CV Mortality, Non-Procedural Bleeding, Stroke, MI



CV Mortality, Ischemic Stroke, MI



Secondary outcomes

	OAC (N=157)	OAC + CLOPIDOGREL (N=156)	RISK RATIO (95% CI)
Death			
Death from any cause	21 (13.4)	24 (15.4)	0.87 (0.51 to 1.50)
Death from cardiovascular causes	13 (8.3)	20 (12.8)	0.65 (0.33 to 1.25)
Stroke			
Ischemic	8 (5.1)	9 (5.8)	0.88 (0.35 to 2.23)
Hemorrhagic	1 (0.6)	0	
Myocardial infarction	1 (0.6)	1 (0.6)	0.99 (0.06 to 15.75)
Bleeding			
Major, life-threatening, or disabling	14 (8.9)	26 (16.7)	0.54 (0.29 to 0.99)
Minor	20 (12.7)	28 (17.9)	0.71 (0.42 to 1.21)

Conclusions POPULAR TAVI COHORT B

In patients with an established indication for OAC undergoing TAVI,

OAC alone as compared to OAC + clopidogrel:

- Reduces the rate of bleeding events, including major, life-threatening, or disabling bleeding
- Does not increase the rate of thrombotic events

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Investigators

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