The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing PCI with stenting

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The WOEST Trial= **W**hat is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing (clinicaltrials.gov NCT00769938)

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Conflict of interest

Investigator-initiated study

Funding:

- **Centre of platelet function research, Sint Antonius Hospital Nieuwegein, The Netherlands**
  Stichting Strect, Tilburg, The Netherlands

Disclosures for JM ten Berg

Consultant	**Merck & Co., Inc**
Speakers' bureau	**Eli Lilly and Company and Merck & Co., Inc.**
Scientific advisory board	**AstraZeneca and Eli Lilly Daiichi Sankyo and Merck & Co., Inc and**

Background

1/ Long term oral anticoagulant therapy (OAC) is obligatory (class I) in:

- most patients with atrial fibrillation
- patients with mechanical heart valves

2/ Over 30% of these patients have concomitant ischemic heart disease. When these patients need to undergo percutaneous coronary stenting, there is also an indication for aspirin and clopidogrel.

3/ Triple therapy (OAC, aspirin and clopidogrel) is recommended according to the guidelines but is also known to increase the risk of major bleeding. Major bleeding increases mortality.

4/ No prospective data available.

Aim of the study

To test the hypothesis that in patients on OAC undergoing PCI, *clopidogrel alone* is superior to the combination *aspirin and clopidogrel* with respect to bleeding but does not increase the thrombotic risk in a multicentre two-country study (The Netherlands and Belgium)

Study Design-1

Inclusion criteria:

1/ Indication for OAC for at least 1 year
2/ One coronary lesion eligible for PCI
3/ Age over 18

Exclusion criteria:

1/ History of intracranial bleeding
2/ Cardiogenic shock during hospitalisation
3/ Peptic ulcer in the previous 6 months
4/ TIMI major bleeding in the previous year
5/ Contra-indication for aspirin or clopidogrel
6/ Thrombocytopenia (platelet count less than 50,000 per ml)
7/ Pregnancy
8/ Age >80

Study Design-2

1:1 Randomisation:

Double therapy group:	Triple therapy group
OAC + 75mg Clopidogrel qd	OAC + 75mg Clopidogrel qd + 80mg Aspirin qd
1 month minimum after BMS 1 year after DES and/or ACS	1 month minimum after BMS 1 year after DES and/or ACS

Follow up: 1 year

Primary Endpoint: The occurence of all bleeding events (TIMI criteria)

Secondary Endpoints:

- Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation
- All individual components of primary and secondary endpoints

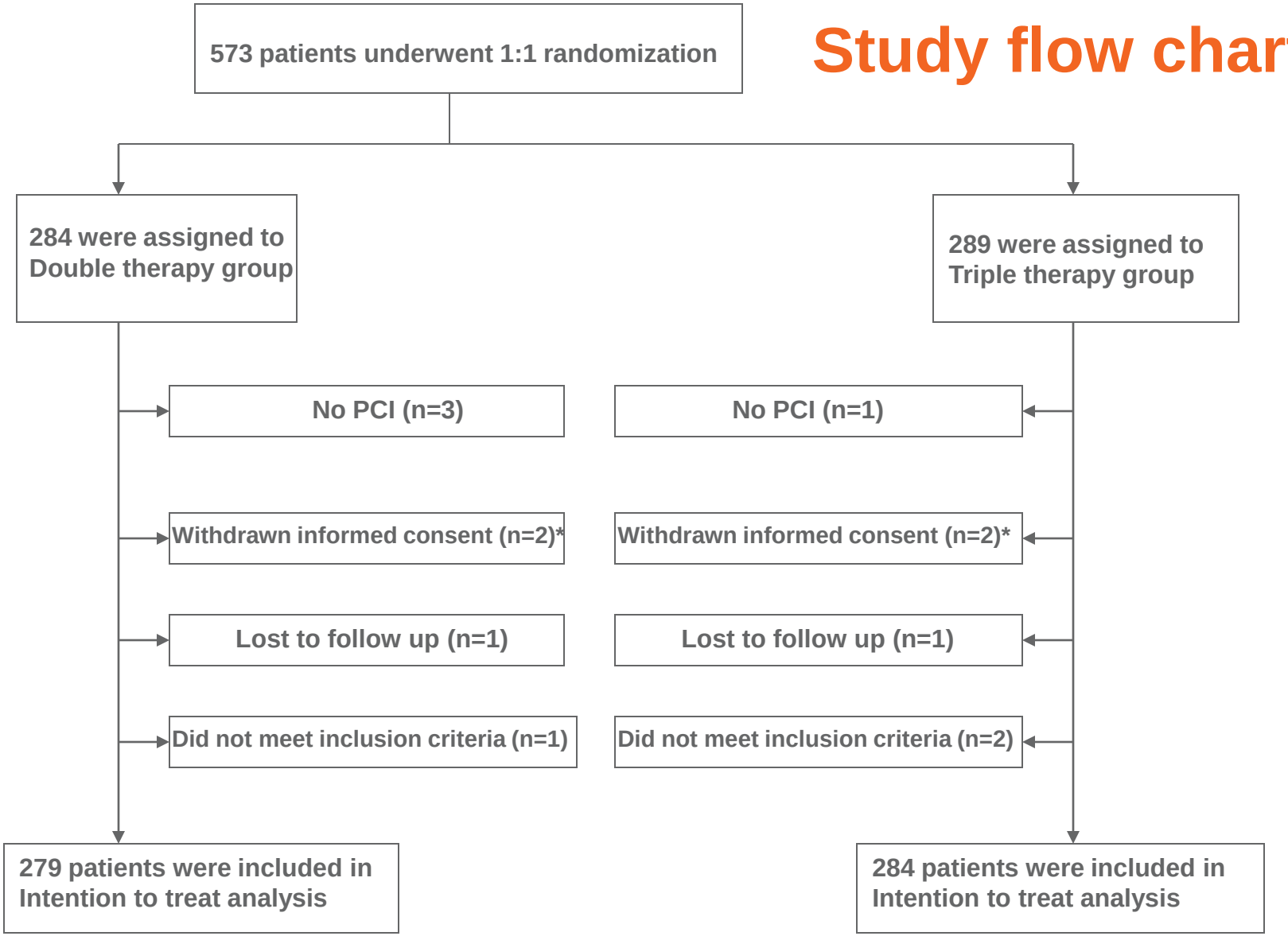
Study Design-3

- Power calculation was based on the largest retrospective study by Karjalainen[1] addressing this issue.
- We anticipated a 12% bleeding rate in the triple therapy group and a 5% bleeding rate in the double therapy group
- Power was chosen to be 80% and α level 5%. The total patient number is estimated at n = 496
- The study is designed as a superiority trial
- All events were adjudicated by a committee blinded to treatment allocation

[1] Eur Heart J 2007;28:726-32

WOEST 15 Dutch and Belgium centers

Study flow chart



* withdrawn informed consent; in double group 2 patients and triple group 1 patient were included in intention to treat analysis until the day of withdrawal

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Baseline Characteristics

	Double therapy n=279 (%)	Triple therapy n=284 (%)
Age	70.3 (±7.3)	69.5(±8.0)
Male gender	214 (76.7%)	234 (82.4%)
BMI (kg/m2)	27.5 (±4.3)	27.9 (±4.2)
Current Smoker	60 (21.5%)	42 (14.8%)
Diabetes	68 (24.4%)	72 (25.4%)
Hypertension	193 (69.2%)	193 (68.0%)
Hypercholesterolemia	191 (68.5%)	205 (72.2%)
History of MI	96 (34.4%)	100 (35.2%)
History of Heart Failure	71 (25.4%)	70 (24.6%)
History of Stroke	49 (17.6%)	50 (17.6%)
History of PCI	86 (30.8%)	101 (35.6%)
History of CABG	56 (20.1%)	74 (26.1%)
History of GI bleeding	14 (5.0%)	14 (4.9%)
Indication for OAC...		
AF/Aflutter	164 (69.5%)	162 (69.2%)
Mechanical valve	24 (10.2%)	25 (10.7%)
Other (pulmonary embolus,	48 (20.3%)	47 (20.1%)
EF<30%, Apical thrombus...)		
ACS at baseline	69 (25.0%)	86 (30.6%)

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Procedural Characteristics

	Double therapy n=279 (%)	Triple therapy n=284 (%)
PCI vessel		
LAD	111(39.9%)	118 (41.8%)
RCX	59 (21.2%)	76 (27.0%)
RCA	92 (33.1%)	72 (25.5%)
Arterial/Venous Graft	16 (5.7%)	16 (5.6%)
INR on the day of PCI	1.86 (±0.9)	1.94 (±1.1)
LVEF <=30%	40 (21.1%)	37 (18.1%)
Stent type		
No	5 (1.8%)	4 (1.4%)
BMS	89 (32.0%)	86 (30.3%)
DES	181 (65.1%)	183 (64.4%)
BMS + DES	3 (1.0%)	11 (3.8%)
Femoral access	204 (73.4%)	208 (74.6%)
Radial access	74 (26.6%)	71 (25.4%)
Angioseal	166 (59.5%)	167 (59.4%)
Other closure device	43 (15.4%)	29 (10.3%)
Peri-produral OAC continuation	128 (45.9%)	113 (39.8%)
Peri-procedural LMWH	66 (23.7%)	68 (23.9%)
Peri-Procedural GPIIbIIIa	25 (8.9%)	26 (9.1%)
Peri-Procedural Fondaparinux	3 (1.0%)	2 (0.7%)

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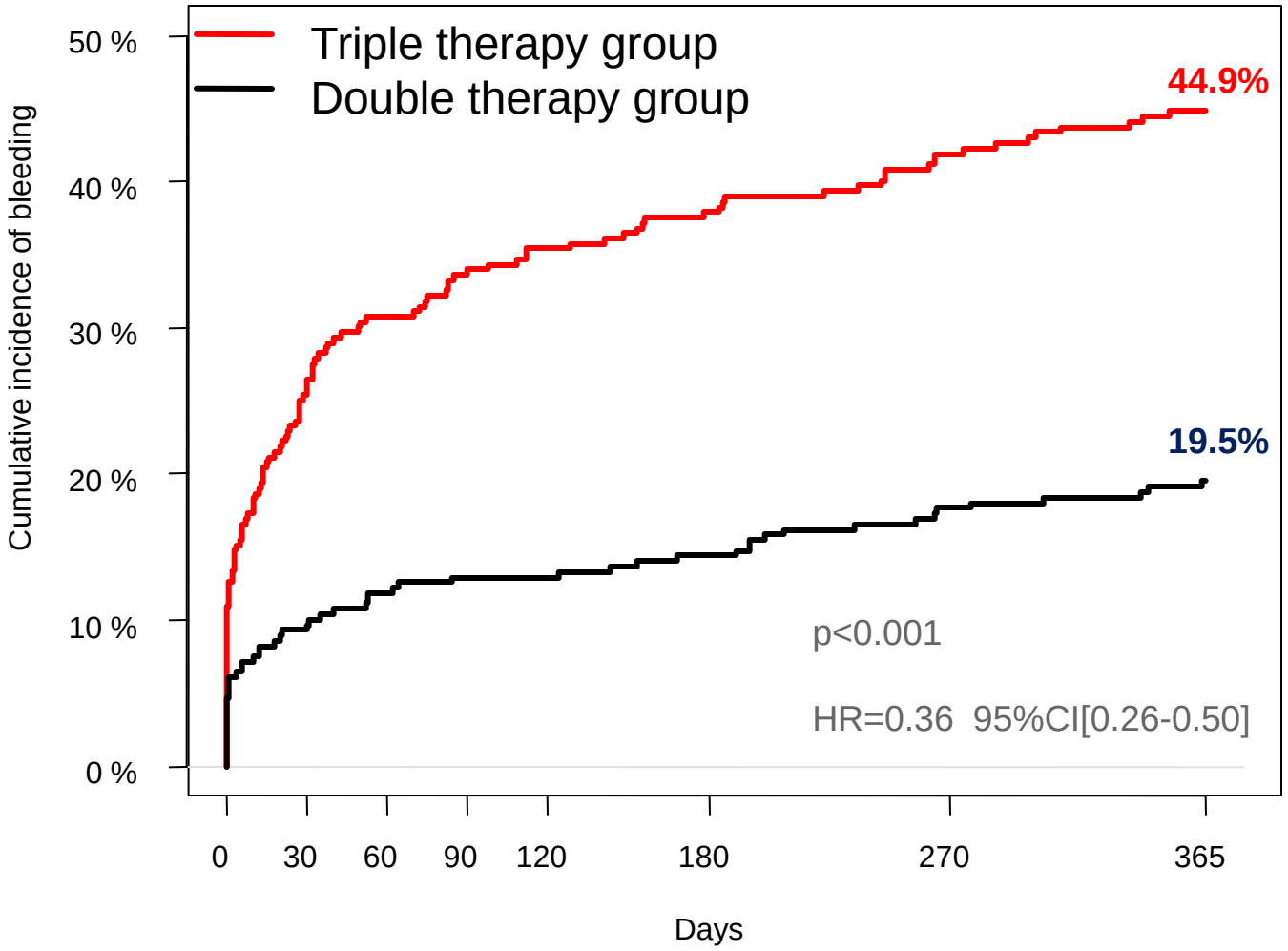
Primary Endpoint: Total number of TIMI bleeding events



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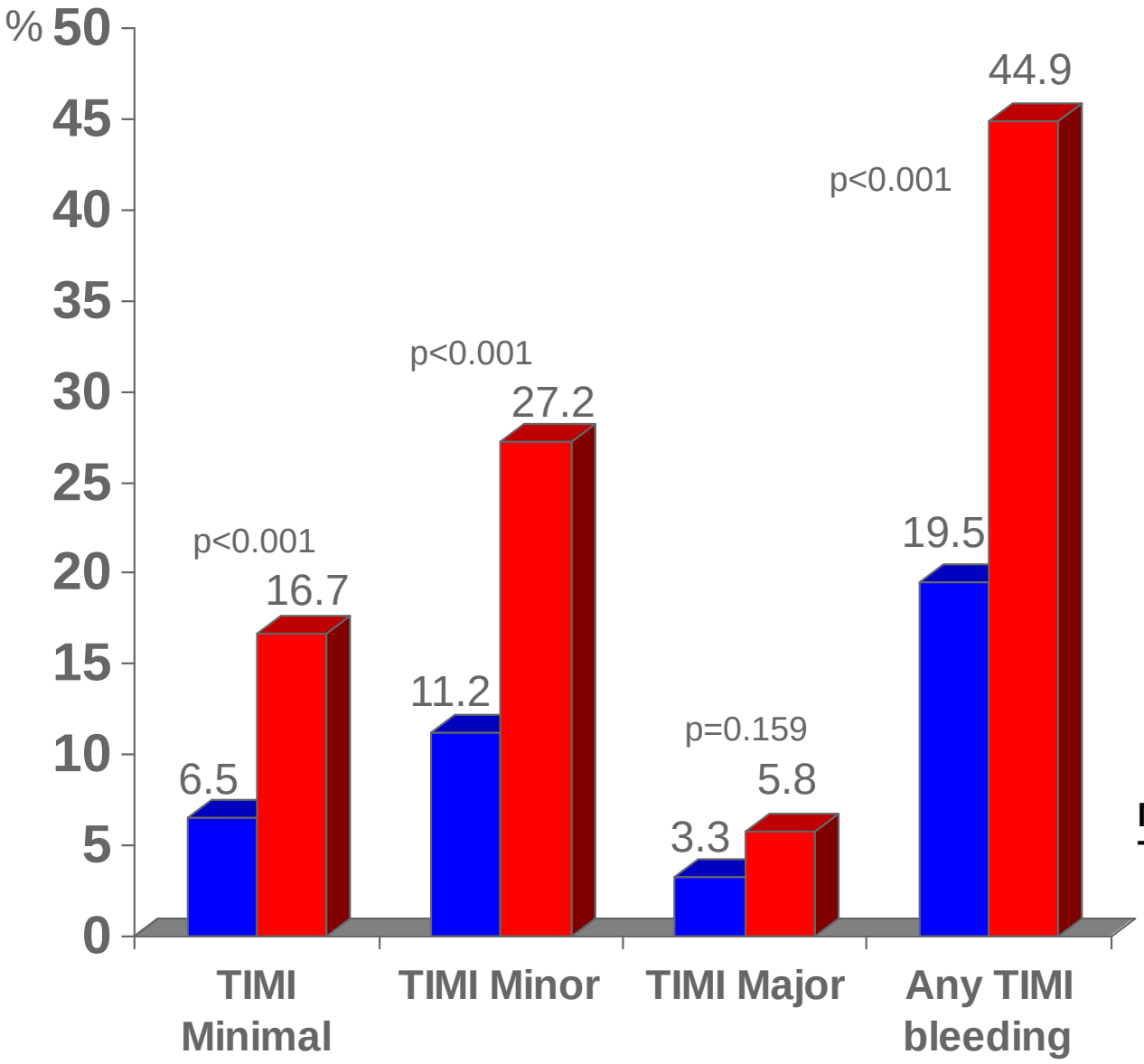
Primary Endpoint: Bleeding events TIMI classification



Double therapy group

Triple therapy group

Multiple bleeds **2.2% vs 12%**
Transfusion **3.9% vs 9.7%**

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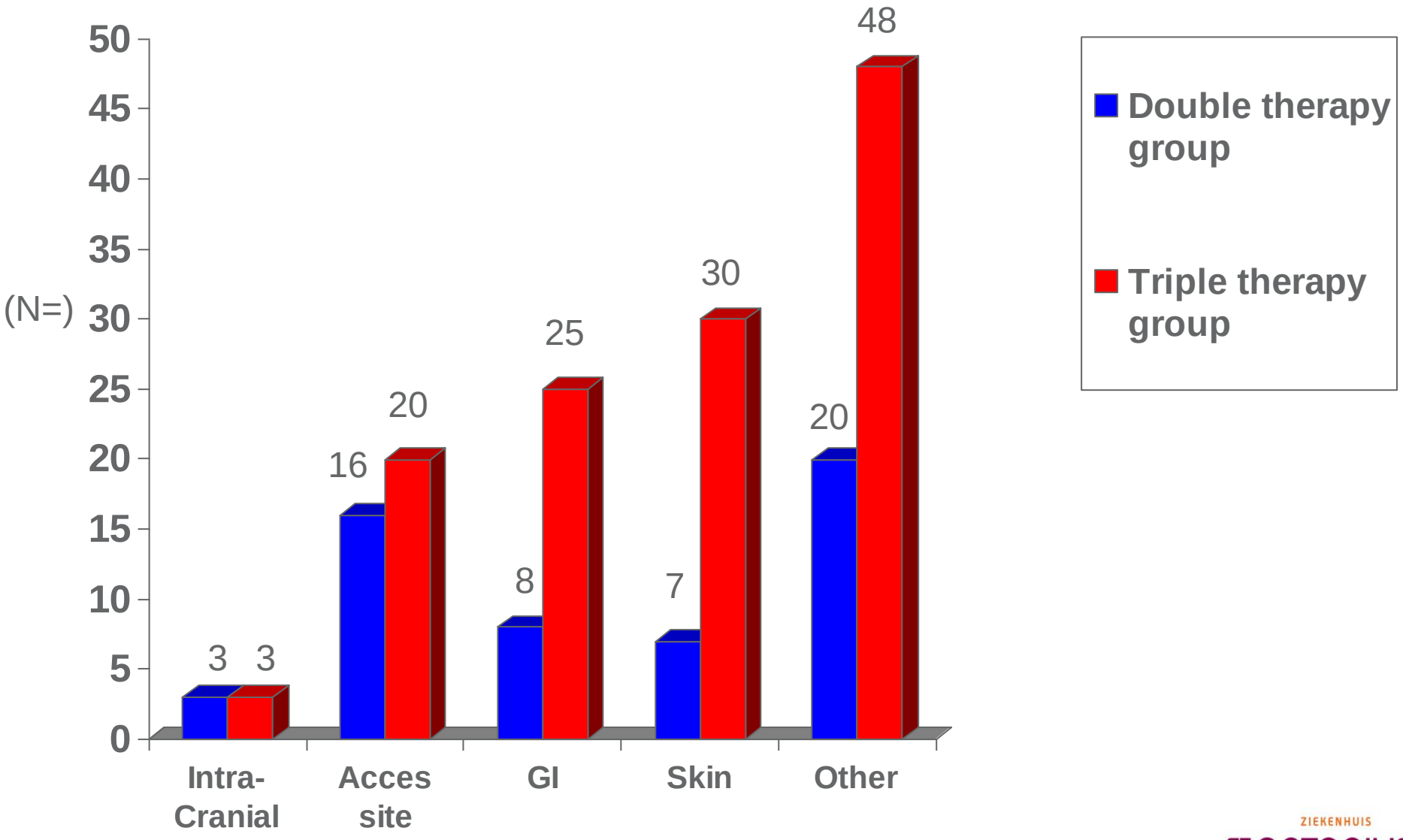
Locations of TIMI bleeding: Worst bleeding per patient



GI=gastro intestinal; Other bleeding consists of eye, urogenital, respiratory tract, retroperitoneal, mouth, PMpocket bleeding

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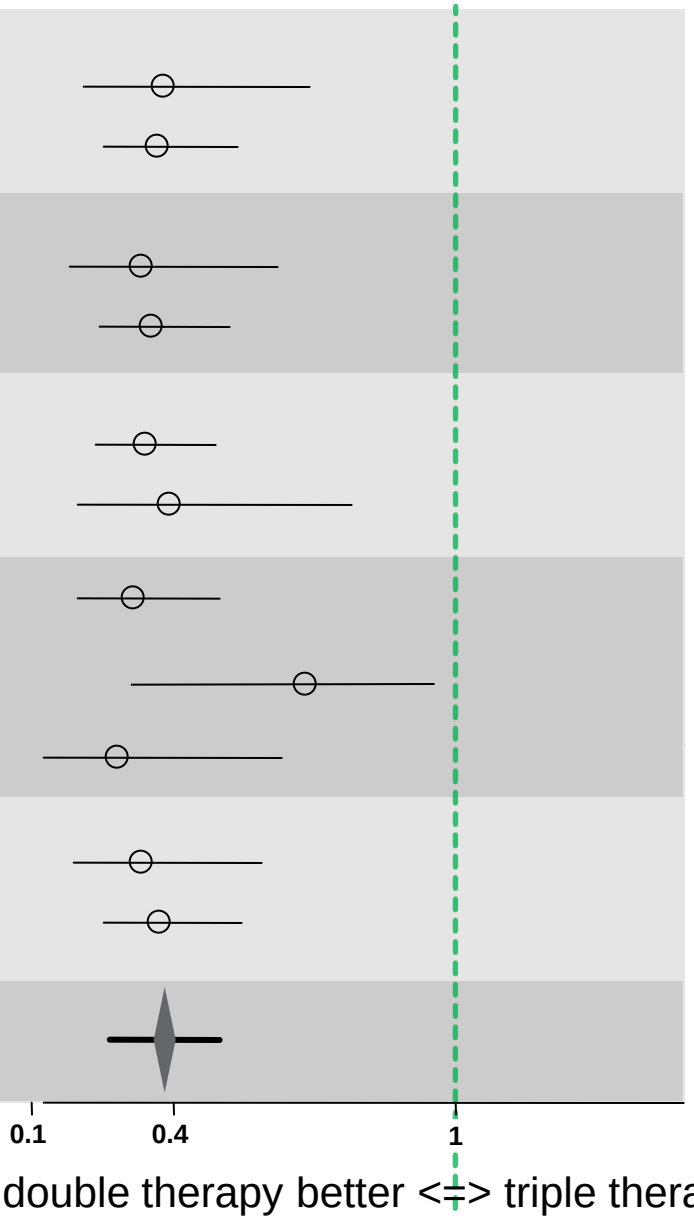
Forest plot of primary endpoint Hazard Ratios

Factor	Group	Triple	Double	P-value for interaction
age	<75 years	79	82	
	>75 years	200	194	0.9157
gender	female	50	65	
	male	234	214	0.8217
ACS	no	195	207	
	yes	86	69	0.7210
indication OAC	AF/AFlut	162	164	
	Mechanical valve	25	24	0.1116
	Other	47	48	0.7761
Stent type	BMS	90	94	
	DES	194	184	0.7894
Overall		**284**	**279**	



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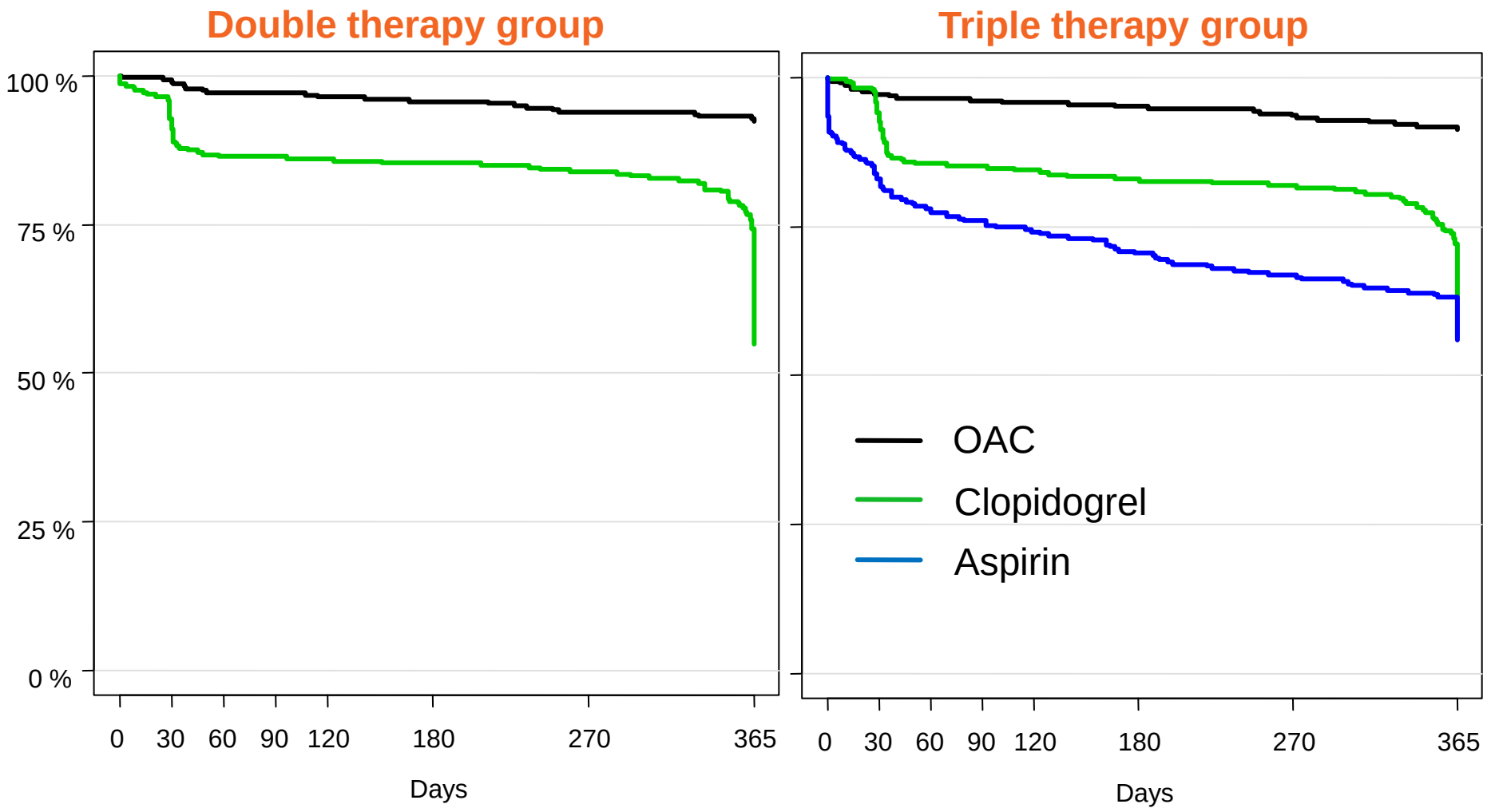
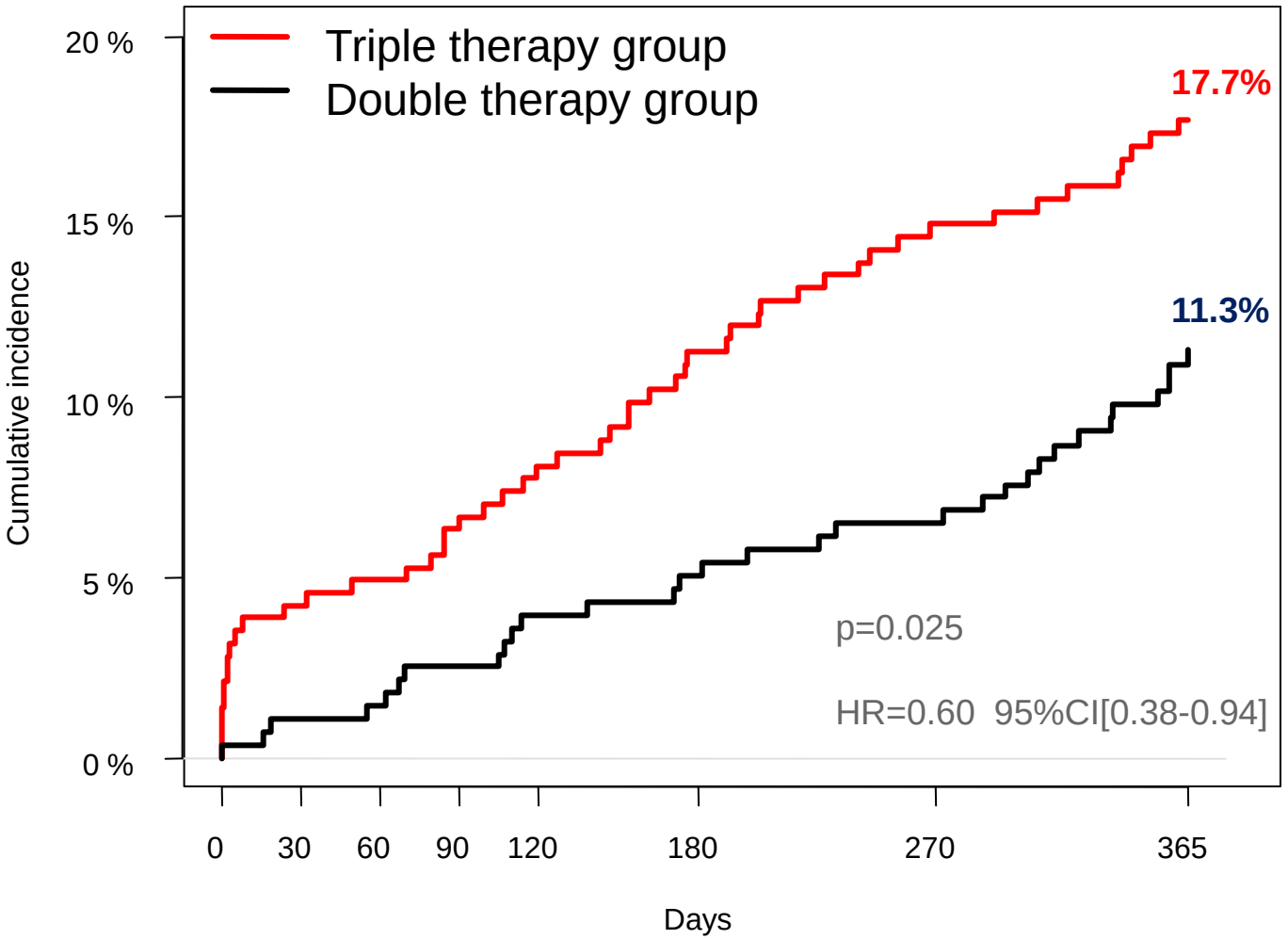
Compliance to OAC, aspirin and clopidogrel



Secondary Endpoint (Death, MI,TVR, Stroke, ST)



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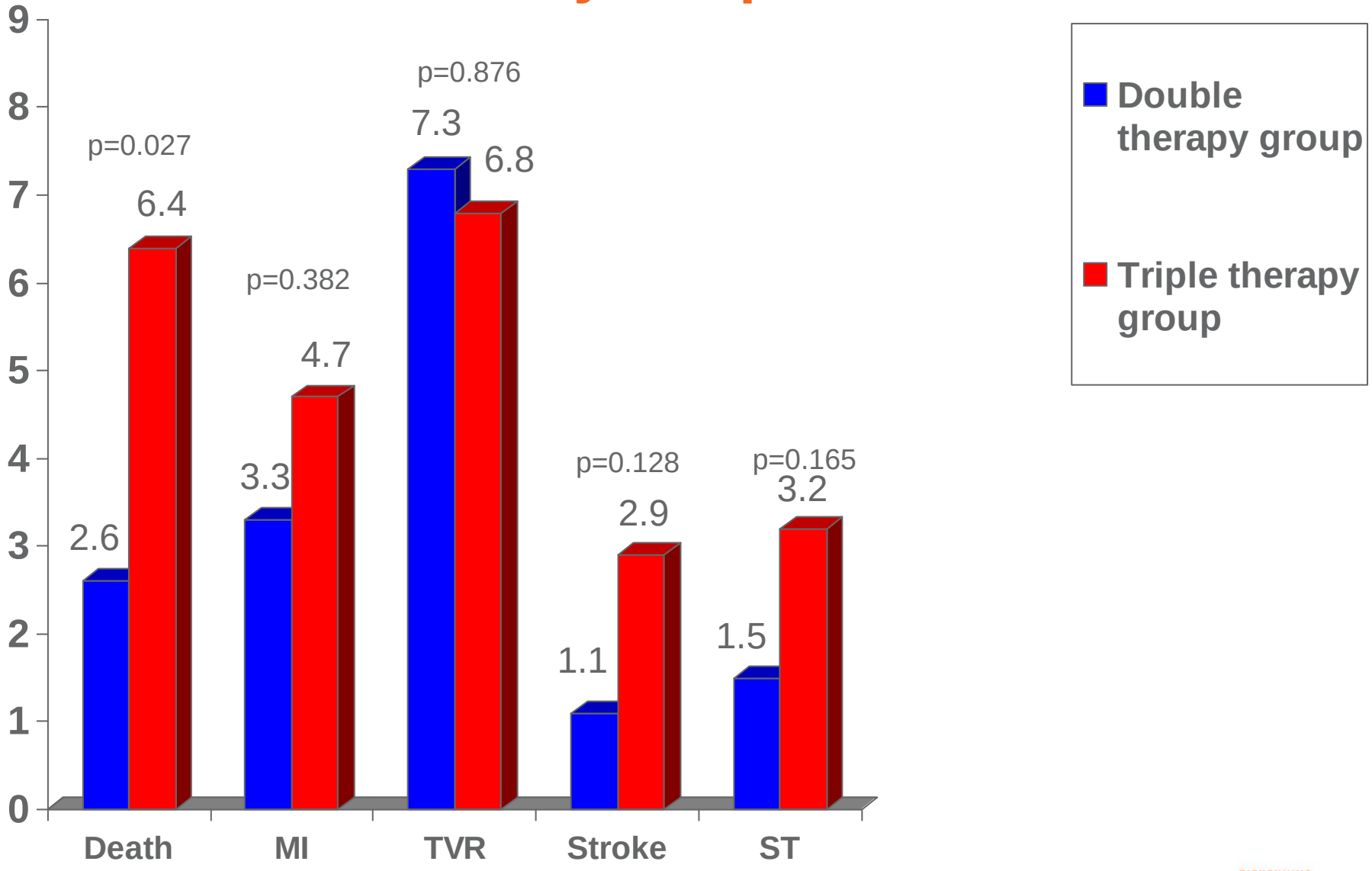
Secondary Endpoint



MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis

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Limitations

- Open label trial design which has its inherent bias

- The study was powered to show superiority on the primary bleeding endpoint, but not to show non-inferiority on the secondary endpoint

- Classification of self reported bleedings for which the patient did not consult a heath-care professional may be subjective

Conclusions

1. In this first randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing PCI the bleeding rate was higher than expected

2. OAC plus clopidogrel causes less bleeding than triple antithrombotic therap. Now shown in a randomized way

3. Double therapydid not lead to an excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death

4. Less all-cause mortality with double therapy

Implications

We propose that clopidogrel alone, without aspirin, is the optimal treatment in high-risk patients on OAC when undergoing PCI

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