

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

Willem Dewilde, Tom Oirbans, Freek Verheugt, Johannes Kelder, Bart De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius Heestermans, Marije Vis, Saman Rasoul, Kaioum Sheikjoesoef, Tom Vandendriessche, Carlos Van Mieghem, Kristoff Cornelis, Jeroen Vos, Guus Brueren, Nicolien Breet and Jurriën ten Berg

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

Conflict of interest

Investigator-initiated study

Funding:

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

Disclosures/Conflict of interest Willem J.M. Dewilde:

none

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 is not increasing 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:

OAC + 75mg Clopidogrel qd

Triple therapy group

OAC + 75mg Clopidogrel qd + 80mg Aspirin qd

1 month minimum after BMS

1 year after DES

1 month minimum after BMS

1 year after DES

Follow up: 1 year

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

Secondary Endpoints:

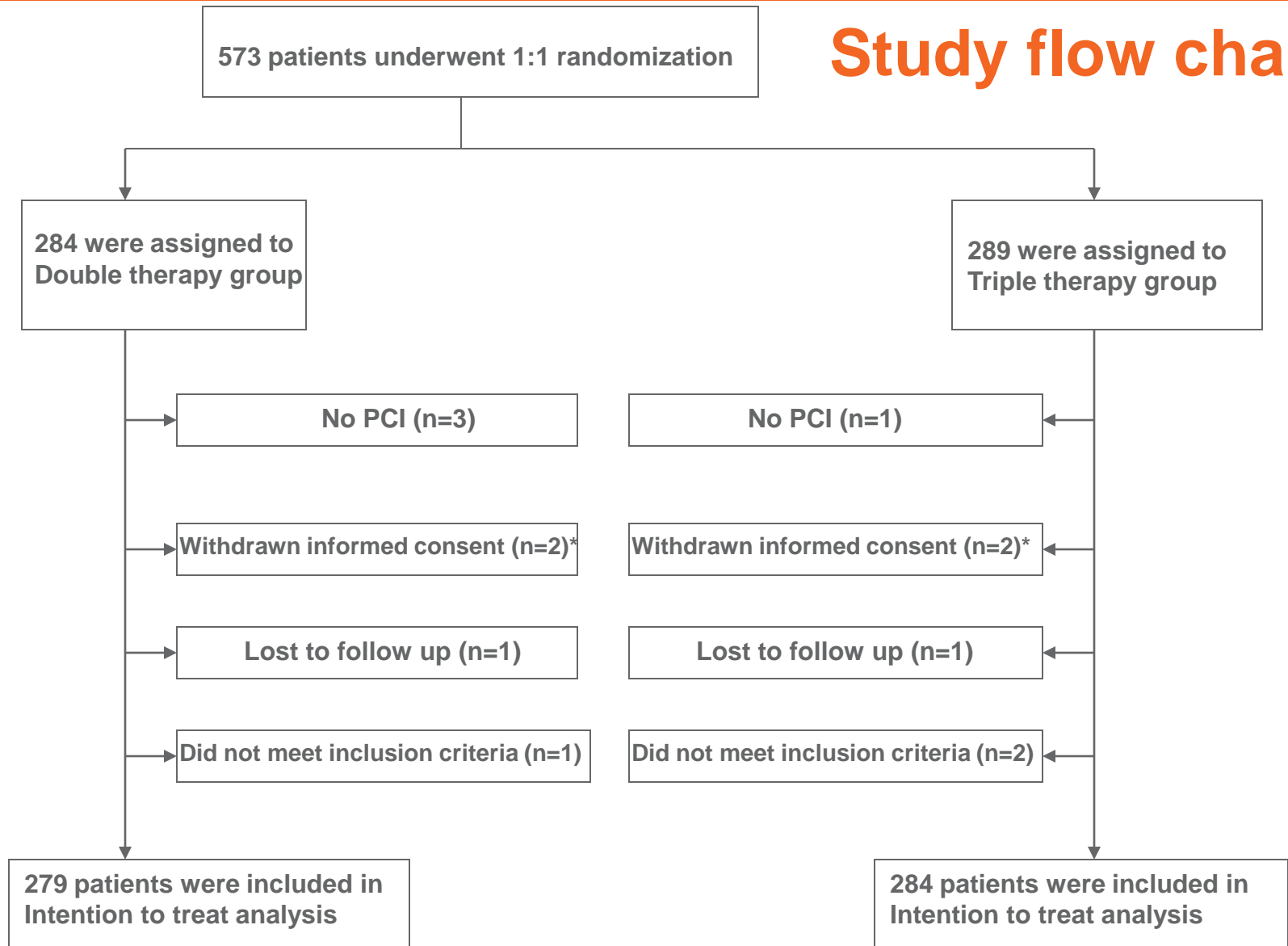
- Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation
- All individual components of primary and secondary endpoints

Study Design-3

- Power calculation was based on the largest retrospective study by Karjalainen¹ 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

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

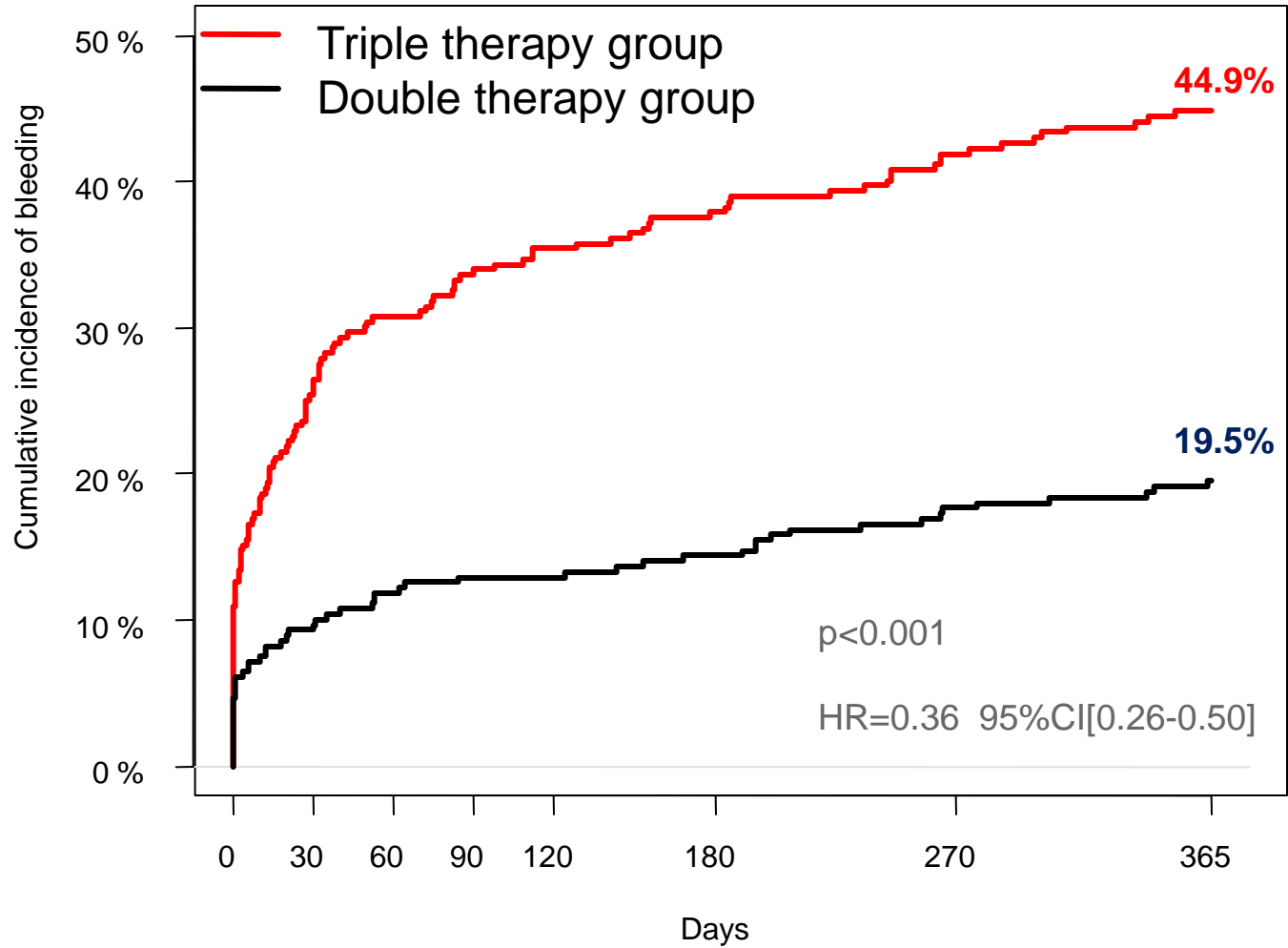
Baseline Characteristics

	Double therapy n=279 (%)	Triple therapy n=284 (%)
Age	70.3 (\pm 7.3)	69.5(\pm 8.0)
Male gender	214 (76.7%)	234 (82.4%)
BMI (kg/m ²)	27.5 (\pm 4.3)	27.9 (\pm 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%)
<i>Indication for OAC</i>		
AF/Aflutter	164 (69.5%)	162 (69.2%)
Mechanical valve	24 (10.2%)	25 (10.7%)
Other (pulmonary embolus, EF<30%, Apical thrombus...)	48 (20.3%)	47 (20.1%)
ACS at baseline	69 (25.0%)	86 (30.6%)

Procedural Characteristics

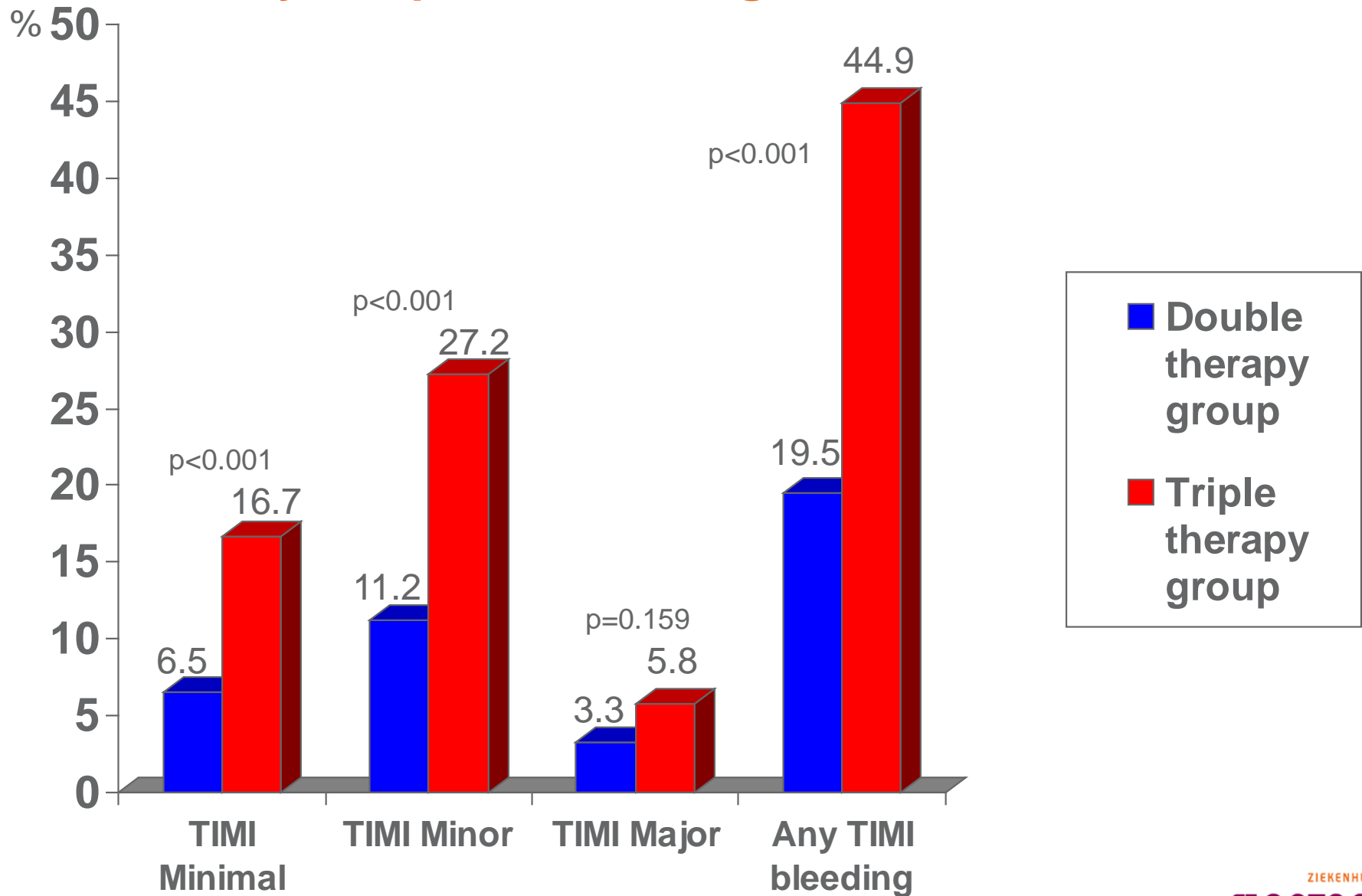
	Double therapy n=279 (%)	Triple therapy n=284 (%)
PCI vessel		
LAD	111 (39.9%)	118 (41.8%)
RCX	59 (21.2%)	76 (27.0%)
RCA	92 (33.1%)	72 (25.5%)
Arterial/Venous Graft	16 (5.7%)	16 (5.6%)
INR on the day of PCI	1.86 (\pm 0.9)	1.94 (\pm 1.1)
LVEF \leq 30%	40 (21.1%)	37 (18.1%)
Stent type		
No	5 (1.8%)	4 (1.4%)
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 GPIIb/IIIa	25 (8.9%)	26 (9.1%)
Peri-Procedural Fondaparinux	3 (1.0%)	2 (0.7%)

Primary Endpoint: Total number of bleeding events (TIMI criteria)

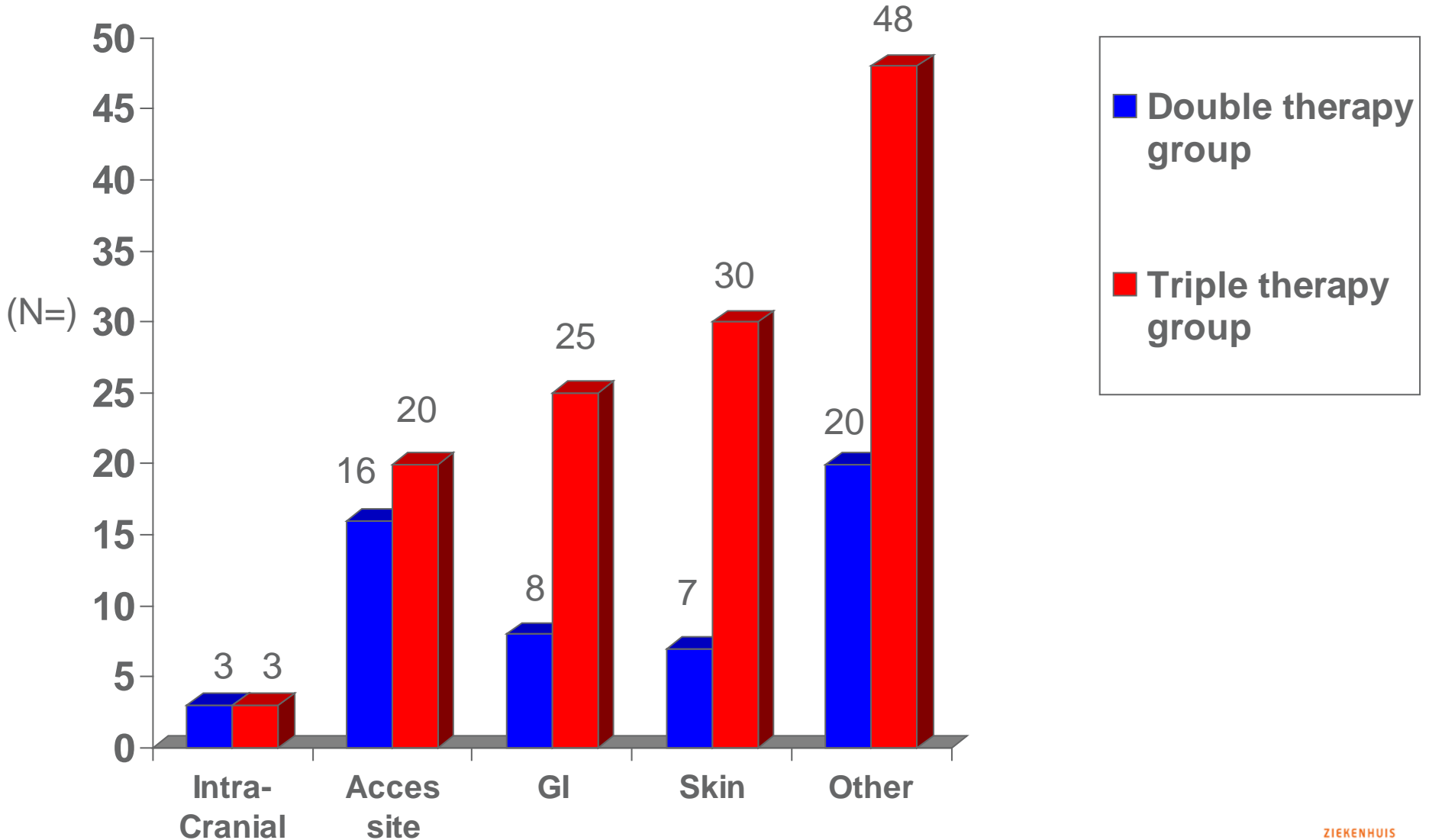


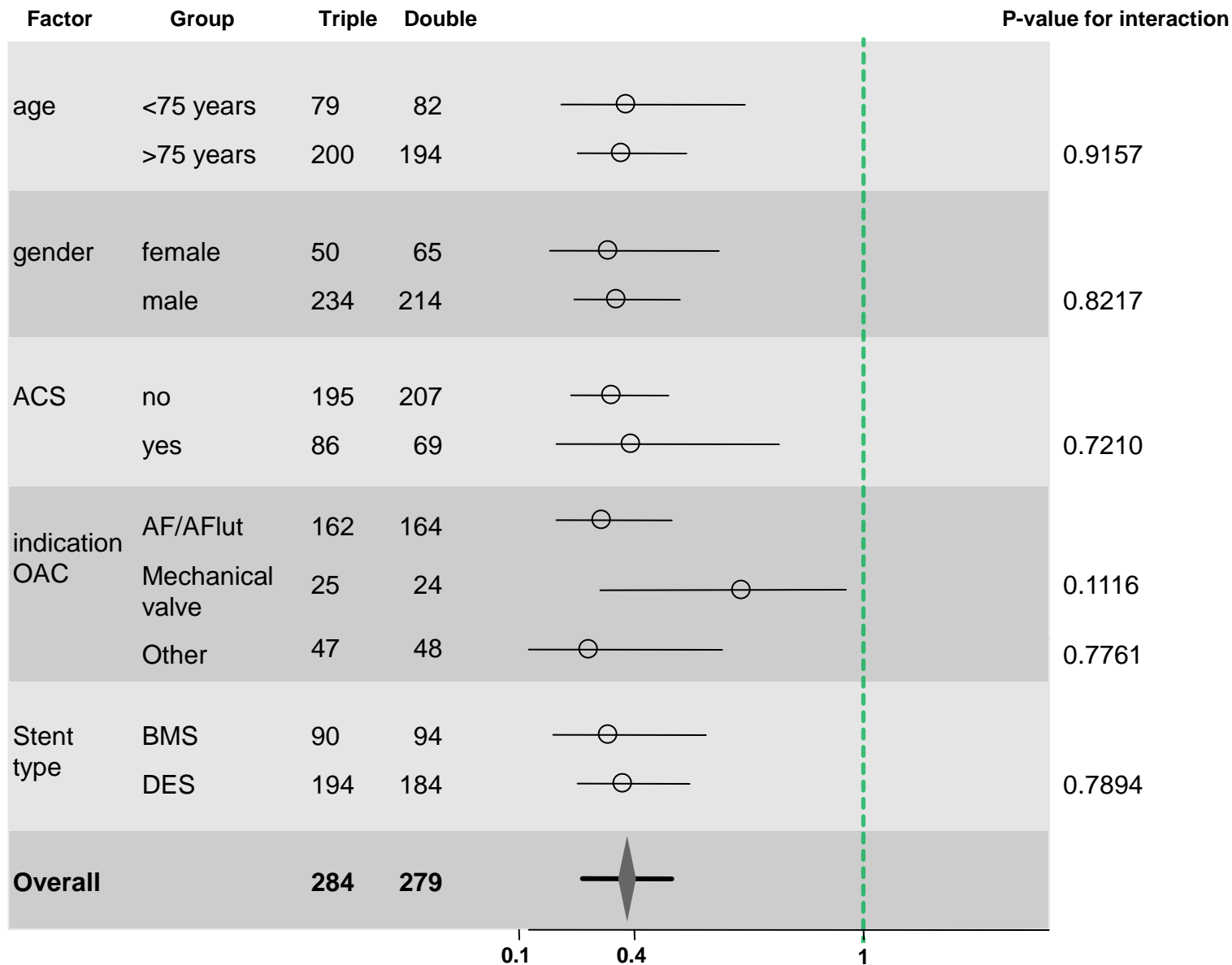
n at risk:	284	210	194	186	181	173	159	140
	279	253	244	241	241	236	226	208

Primary Endpoint: Bleeding events TIMI classification



Locations of TIMI bleeding: Worst bleeding per patient



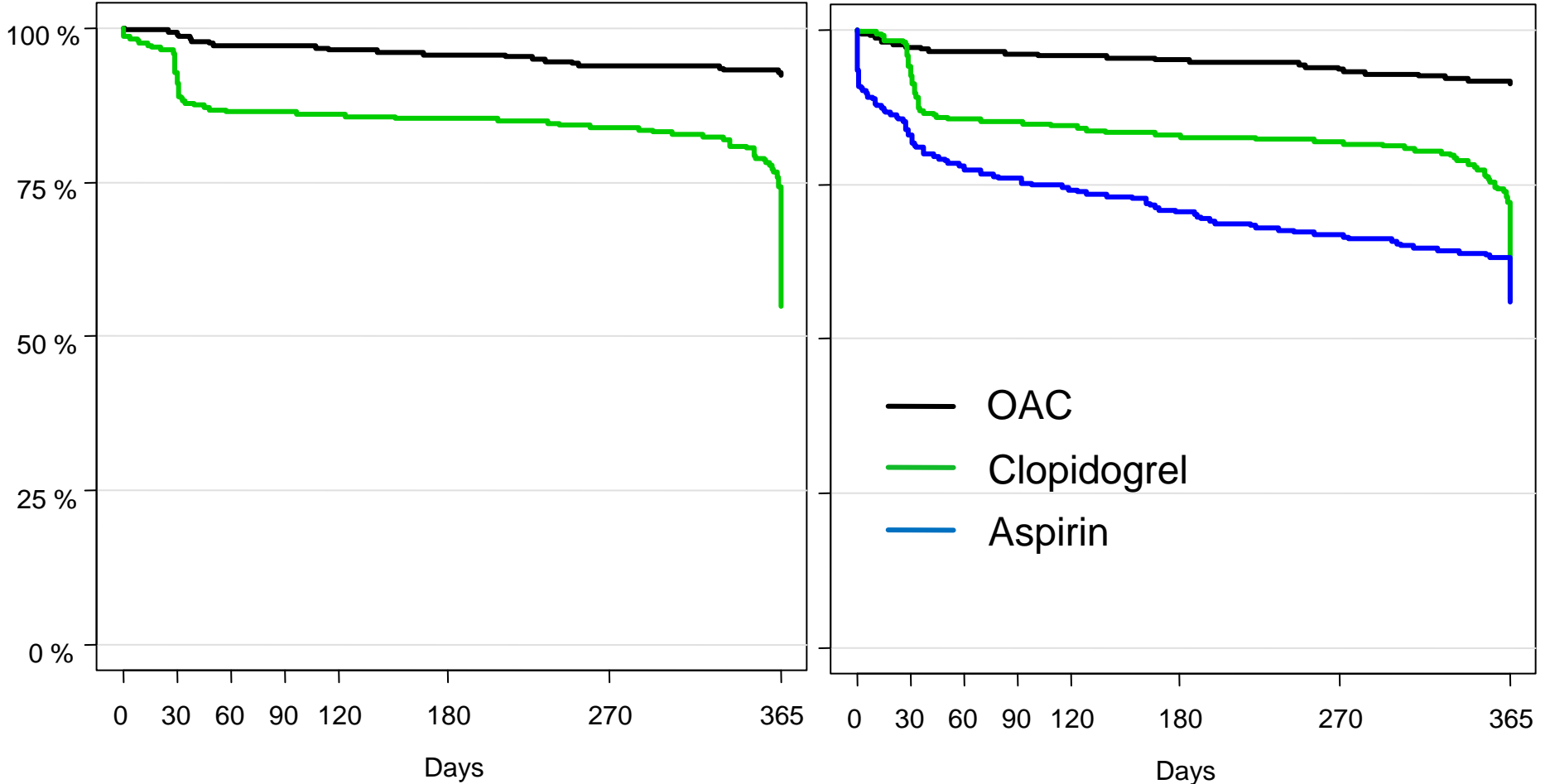


0.1 0.4 1
 double therapy better \Leftrightarrow triple therapy better

Compliance to OAC, aspirin and clopidogrel

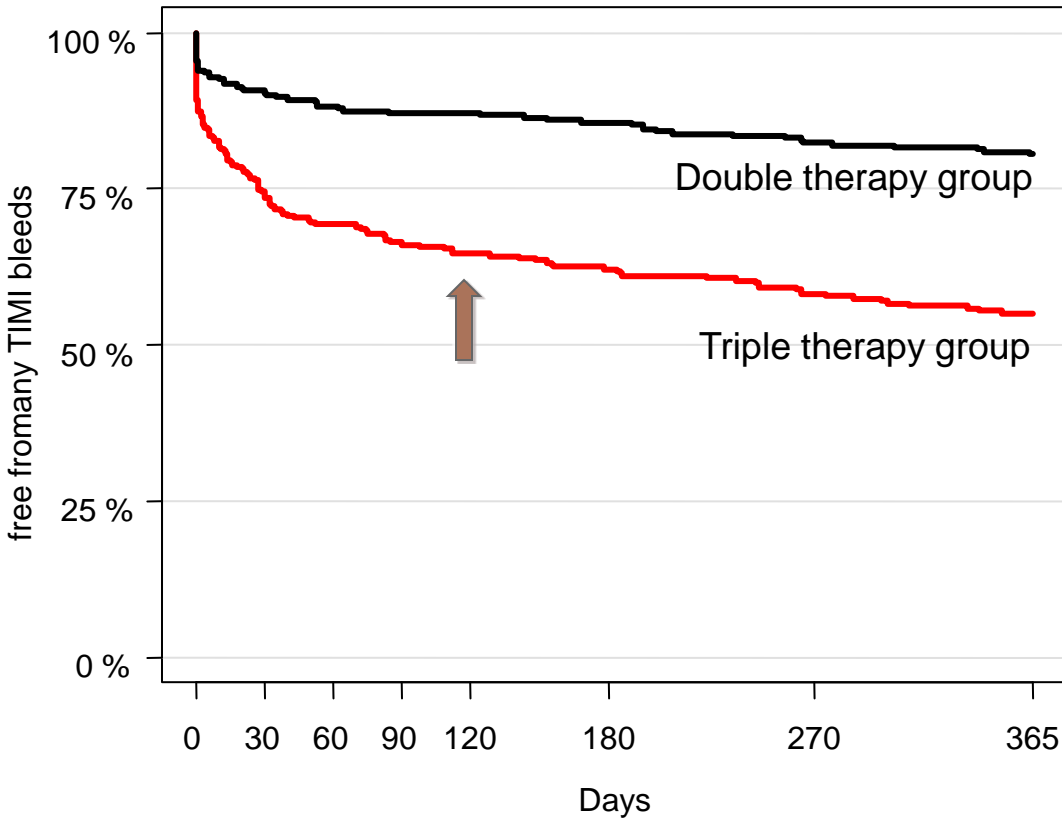
Double therapy group

Triple therapy group

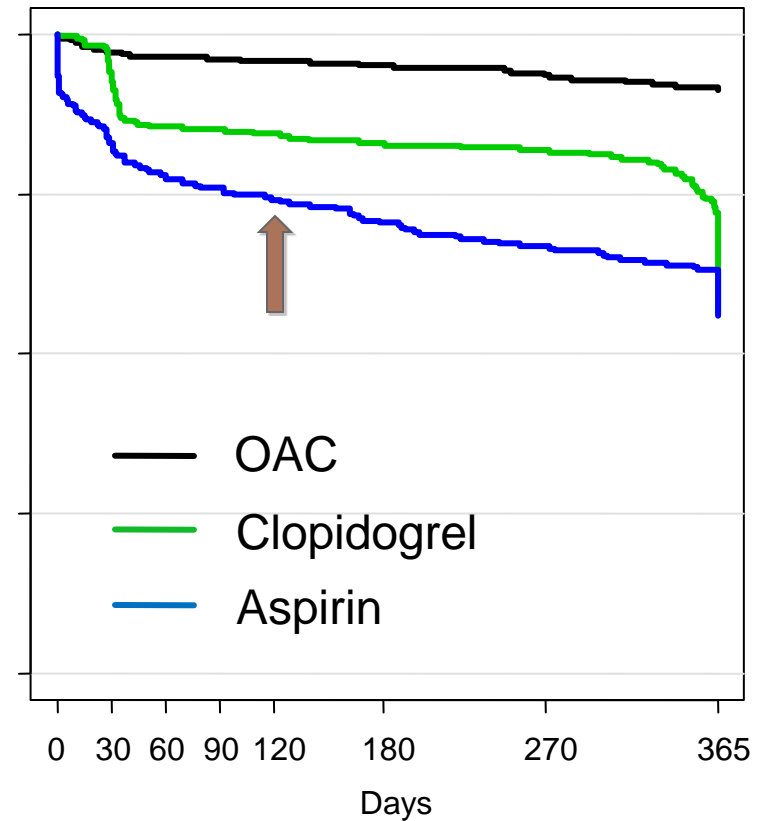


Bleeding in triple therapy group and aspirin compliance

Free from bleeding curve

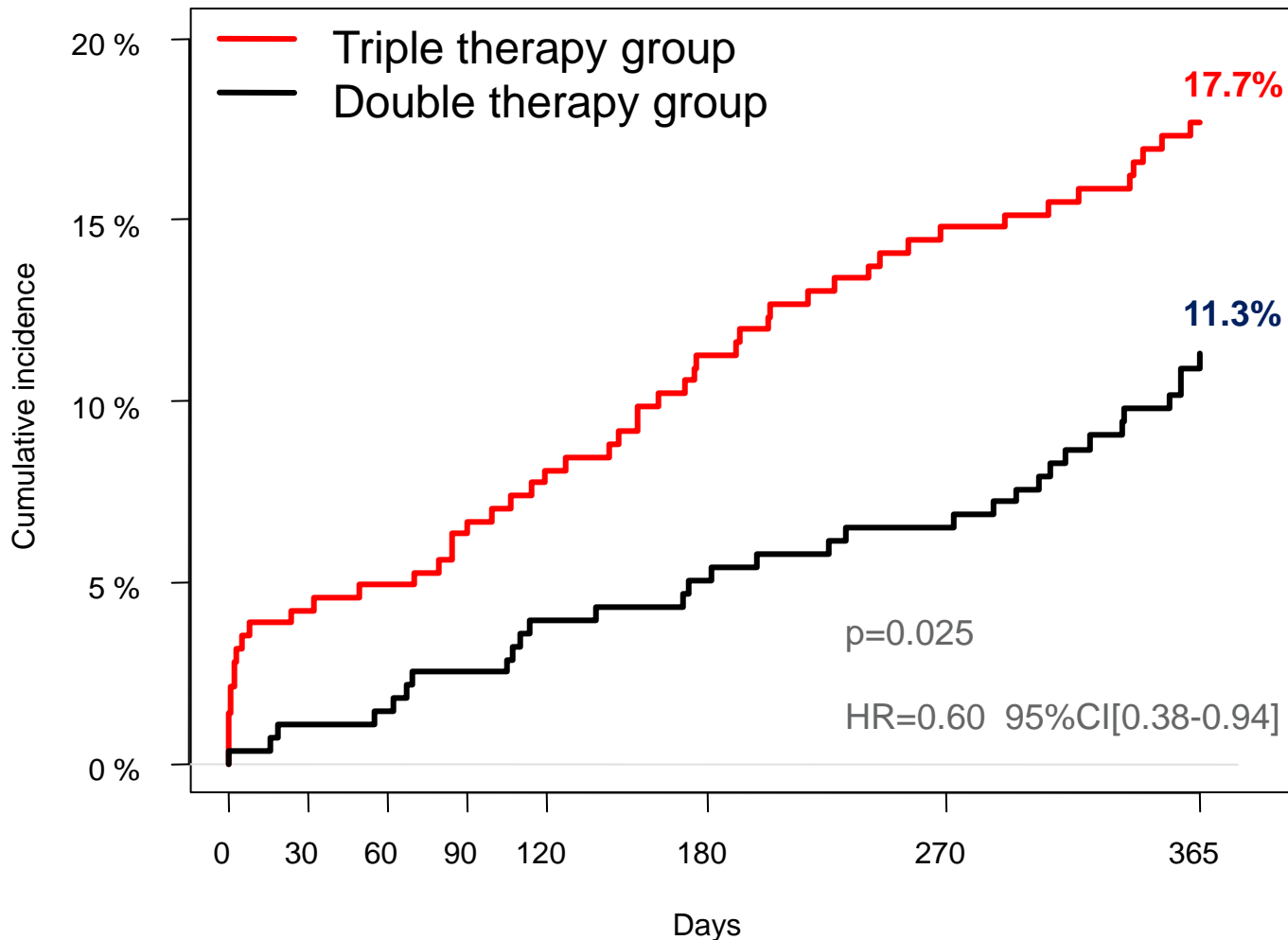


Triple therapy group



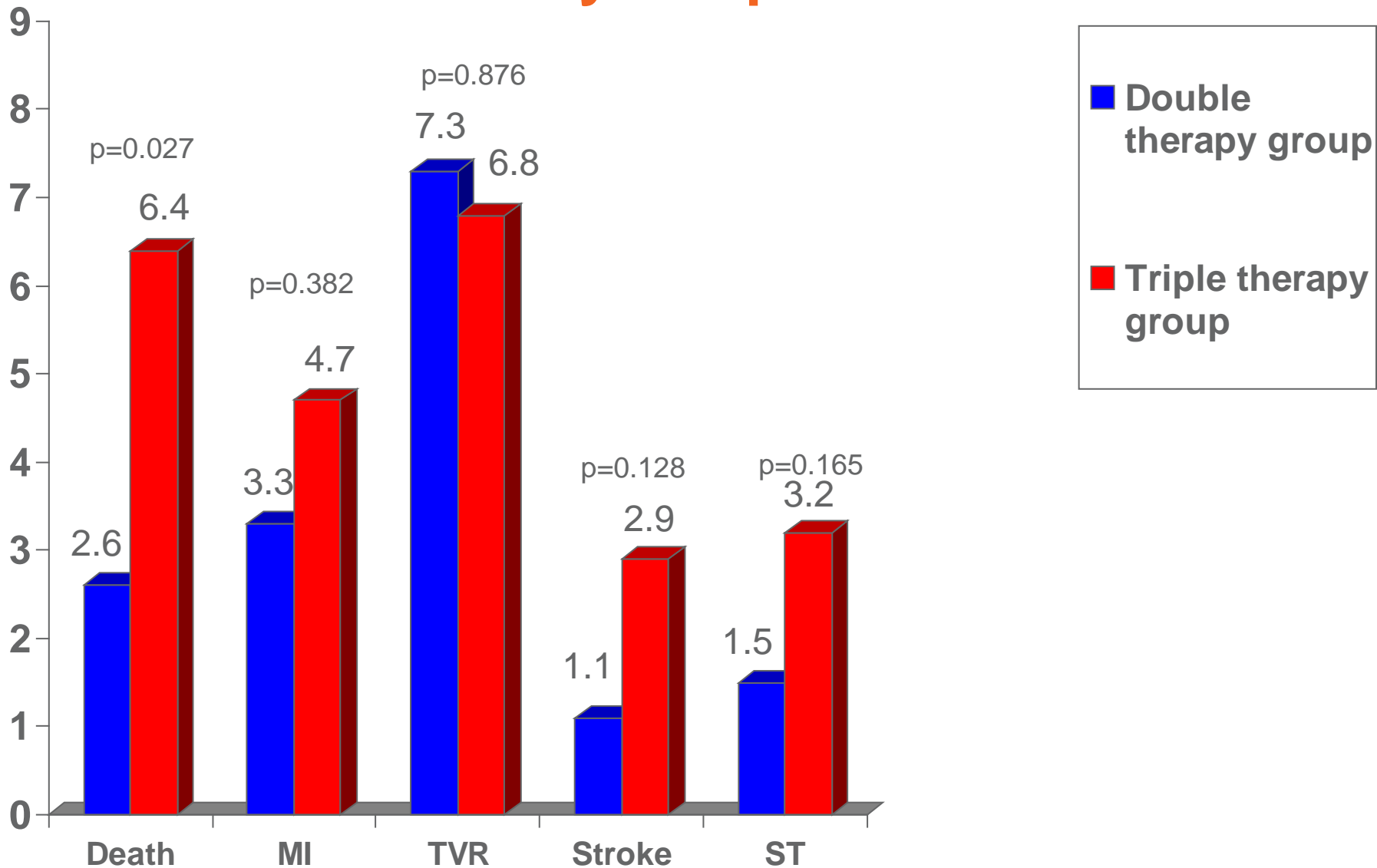
n at risk: 284 210 194 186 181 173 159 140
 279 253 244 241 241 236 226 208

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



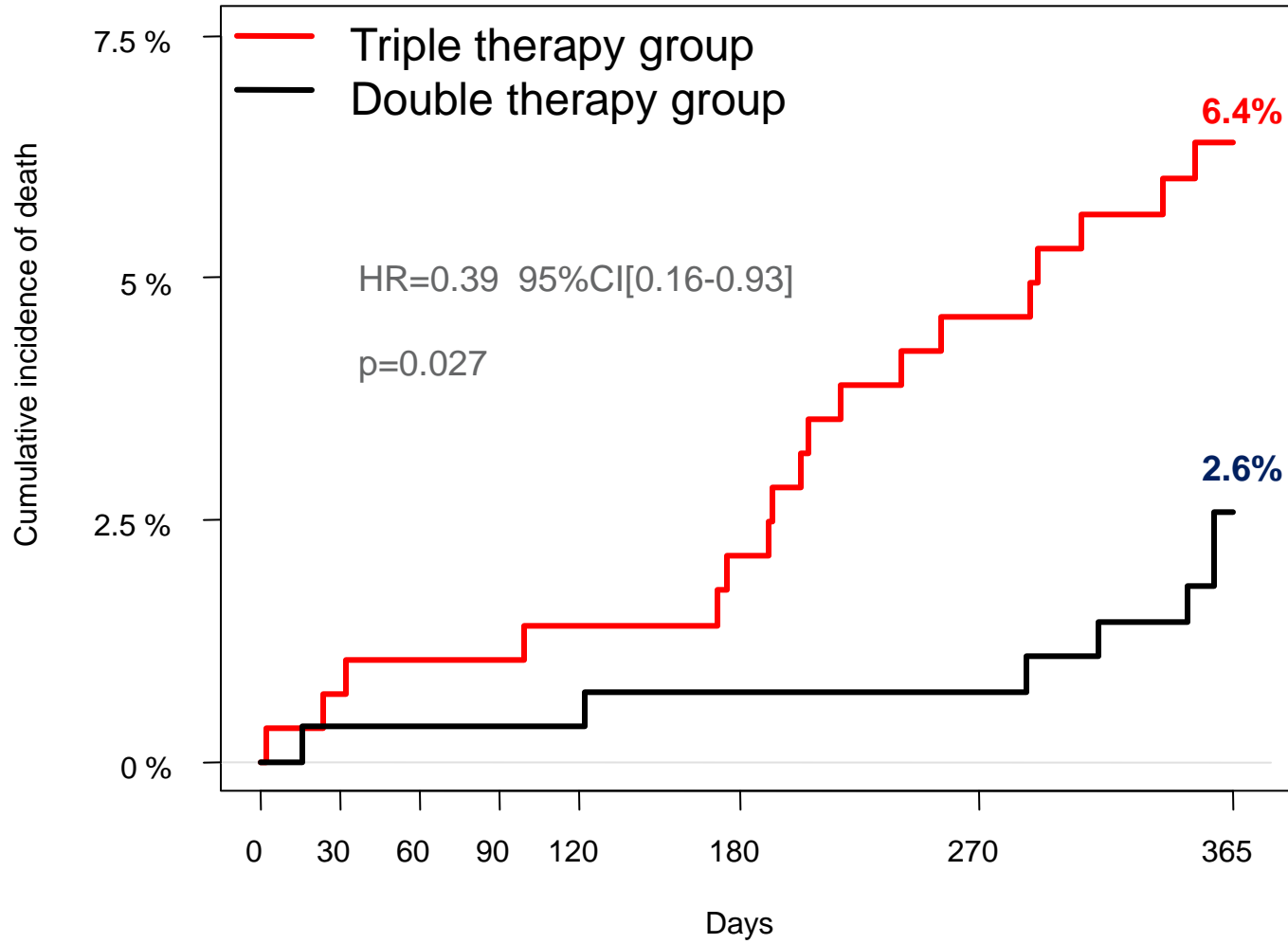
n at risk:	284	272	270	266	261	252	242	223
	279	276	273	270	266	263	258	234

Secondary Endpoint



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

All-Cause Mortality



n at risk:	284	281	280	280	279	277	270	252
	279	278	276	276	276	275	274	256

Limitations

- **The study was powered to show superiority on the primary bleeding endpoint, but not to show non-inferiority on the secondary endpoint**
- **Open label trial design with its inherent bias**
- **Classification of smaller bleeding, although well defined and blindly adjudicated, may be subjective**

Conclusions

1. First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting
2. In this study which was specifically designed to detect bleeding events, the bleeding rate was higher than expected
3. Primary endpoint was met: OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy, but now shown in a randomized way
4. Secondary endpoint was met: with double therapy there is no excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death
5. Less all-cause mortality with double therapy

Implications

We propose that a strategy of oral anticoagulants plus clopidogrel, but without aspirin could be applied in this group of high-risk patients on OAC when undergoing PCI

The WOEST investigators

TweeSteden Hospital, Tilburg: **Willem Dewilde, Wilbert Aarnoudse**

Centre of platelet function research, Sint Antonius Hospital Nieuwegein: **Nicolien Breet, Tom Oirbans, Jur ten Berg, Hans Kelder, Mike Bosschaert, Thomas Bergmeijer, Paul Janssen**

University Medical Center Groningen, Groningen **Bart De Smet**

Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam: **Jean-Paul Herrman, Freek Verheugt**

Catholic University of Leuven, Leuven: **Tom Adriaenssens**

Hospital Oost-Limburg (ZOL), Belgium: **Mathias Vrolix**

Medical Center Alkmaar, Alkmaar: **Ton Heestermans**

Academic Medical Center, University of Amsterdam, Amsterdam: **Marije Vis**

Isala Hospital, Zwolle: **Arnoud van 't Hof, Saman Rasoul**

Maasstad Ziekenhuis, Rotterdam: **Kaioum Sheikjoesoef**

University Hospital Antwerp, Antwerp: **Tom Vandendriessche**

Hospital Maria Midderalers, Gent: **Kristoff Cornelis**

Onze lieve Vrouw Ziekenhuis Aalst: **Carlos van Mieghem**

Amphia Hospital, Breda: **Jeroen Vos**

Catharina Hospital, Eindhoven: **Guus Brueren**