Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation (ISAR-TRIPLE Trial)

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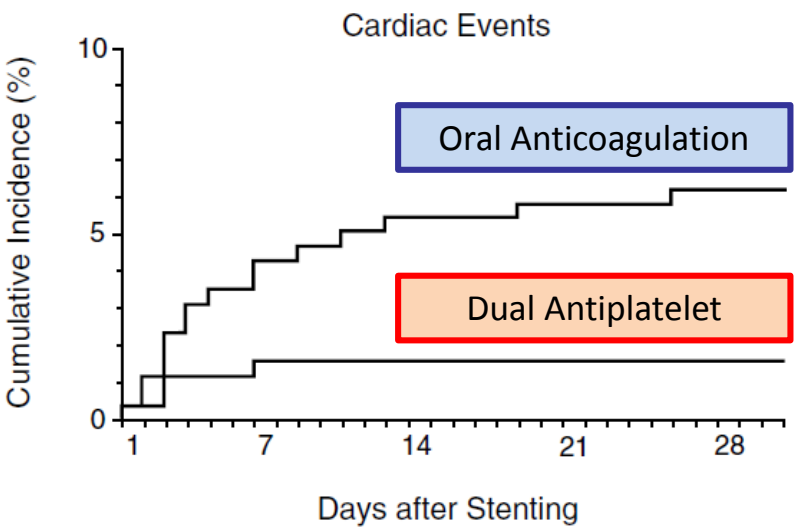
Background

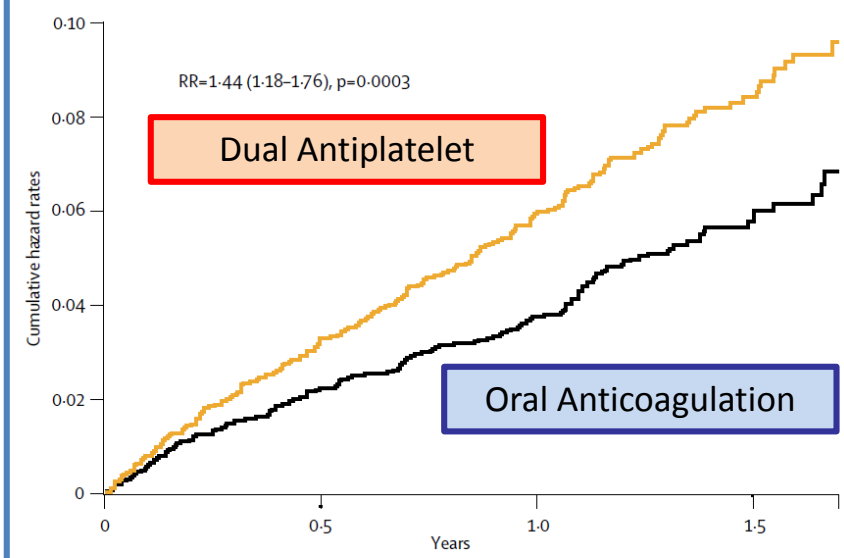
Coronary stent implantation



ISAR, NEJM 1996

+

Atrial fibrillation



ACTIVE-W Lancet 2006

= Dual Antiplatelet + Oral Anticoagulation

Schömig et al. NEJM 1996;334:1084-9.
Connolly et al. Lancet 2006;367:1903-12.

Background

- **Such triple therapy increases the risk of bleeding however.**

- **The optimal duration of triple therapy after drug-eluting stent (DES) implantation has not been defined. Two factors need to be considered in this regard:**

  1. The risk of stent thrombosis is highest in the early phase after PCI and declines over time

  2. The risk of bleeding is dependent on length and intensity of OAC therapy

Lip et al. Eur Heart J. 2014 Aug 25. pii: ehu298

Objective

To evaluate clinical outcomes of a therapy duration of

6 weeks clopidogrel

versus

6 months clopidogrel

after DES implantation in patients receiving concomitantly aspirin and oral anticoagulation

ISAR-TRIPLE: Study Organization

DESIGN:
Prospective, randomized open-label trial

INCLUSION CRITERIA:
DES implantation and indication for oral anticoagulation

MAJOR EXCLUSION CRITERIA:
Previous stent thrombosis
DES in left main coronary artery

SPONSOR:
Deutsches Herzzentrum Munich, (ClinicalTrials.gov # NCT00776633)

614 patients with DES implantation
3 European centers
(September 2008 – December 2013)

Aspirin and VKA

6-week Clopidogrel (n=307)

6-month Clopidogrel (n=307)

Clinical follow up at 9 months in 606 patients (98.7%)

VKA: Vitamin K Antagonist

ISAR-TRIPLE: Study Organization

TEST HYPOTHESES:

6-week superior to 6-month therapy; Primary Endpoint 10%, Risk reduction 60% with 6-week therapy; Power = 80%, alpha = 0.05; 283 patients per group

PRIMARY ENDPOINT:

- Death, myocardial infarction, definite stent thrombosis, stroke or TIMI major bleeding at 9 months

SECONDARY ENDPOINTS:

- Ischemic complications: Cardiac death, myocardial infarction, definite stent thrombosis or ischemic stroke
- Bleeding complications (TIMI major)

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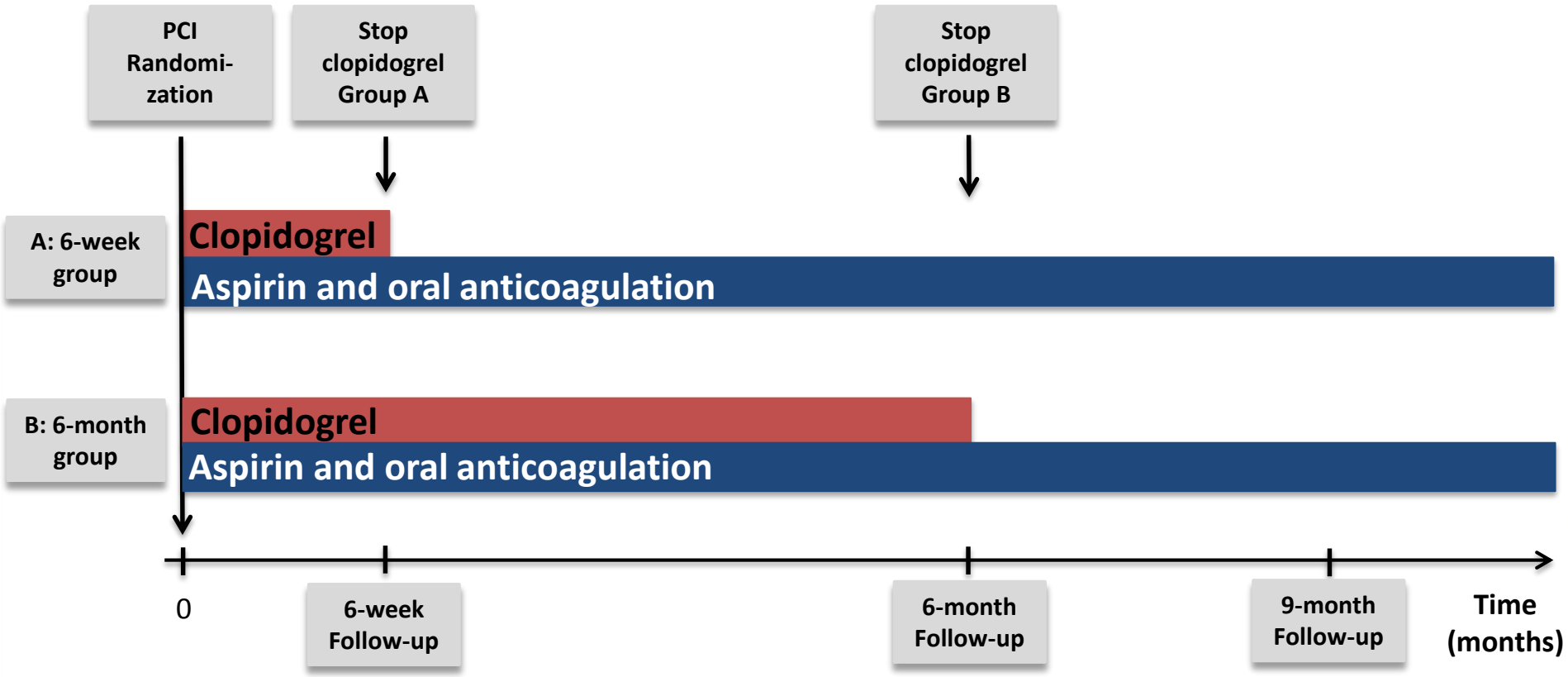
Randomization



Fiedler et al. Am Heart J. 2014; 167(4):459-465

ISAR-TRIPLE Investigators

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- **Klinikum rechts der Isar, Munich, Germany:** Petra Hoppmann, Simon Schneider, Tareq Ibrahim, Karl-Ludwig Laugwitz
- **Klinikum der Ludwig Maximilians Universität, Munich, Germany:** Julinda Mehilli, Dirk Sibbing, Steffen Massberg, Nikolaus Sarafoff

Baseline Characteristics

		6-week group (n=307)	6-month group (n=307)
Age (years)		74 ± 8	73 ± 9
Female sex		25 %	21 %
Diabetes		28 %	23 %
History of myocardial infarction		29 %	25 %
Clinical presentation	ACS	33 %	31 %
	Stable Angina	67 %	69 %
Indication for OAC *	Atrial fibrillation	83 %	85 %
	Mechanical valve	5 %	9 %
	VTE	7 %	4 %
	other	4 %	2 %

*p=0.03; OAC= Oral Anticoagulation; VTE= Venous Thrombembolism

Antithrombotic therapy

ASPIRIN:
75-200 mg per day
CLOPIDOGREL:
75 mg per day
PHENPROCOUMON or WARFARIN:
Target INR 2.0 or 2.5 in patients with mechanical valves

Compliance	6-week FU		6-month FU		9-month FU	
Aspirin*	97 %		95 %		96 %	
OAC*	94 %		91 %		88 %	
INR (median)*	2.2		2.3		2.3	
Time in therapeutic range *	64 %		69 %		66 %	
Clopidogrel 6-week group	97 %	P=0.56	26 %	P<0.001	23 %	P<0.001
Clopidogrel 6-month group	98 %		87 %		35 %	

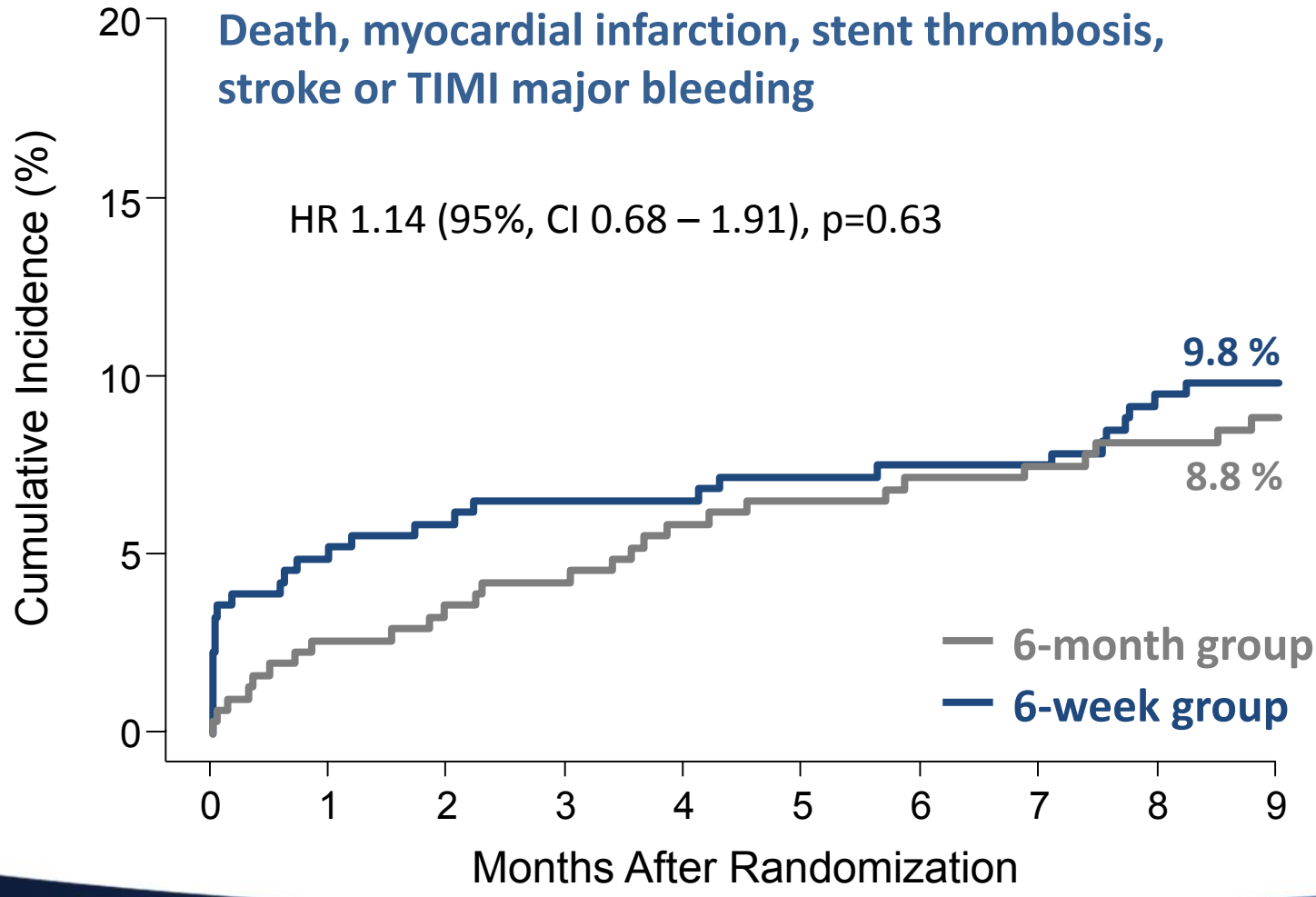
*No significant differences between groups; FU= Follow Up time point

Stent type

	6-week group (417 lesions)	6-month group (409 lesions)
2nd gen. permanent polymer DES	203 (48.7)	206 (50.4)
Biodegradable polymer DES	131 (31.4)	134 (32.8)
Polymer free DES	45 (10.8)	46 (11.2)
1st gen. permanent polymer DES	29 (6.9)	16 (3.9)
BVS	4 (1.0)	3 (0.7)
BMS*	2 (0.5)	0
DEB/PTCA**	3 (0.7)	4 (1.0)

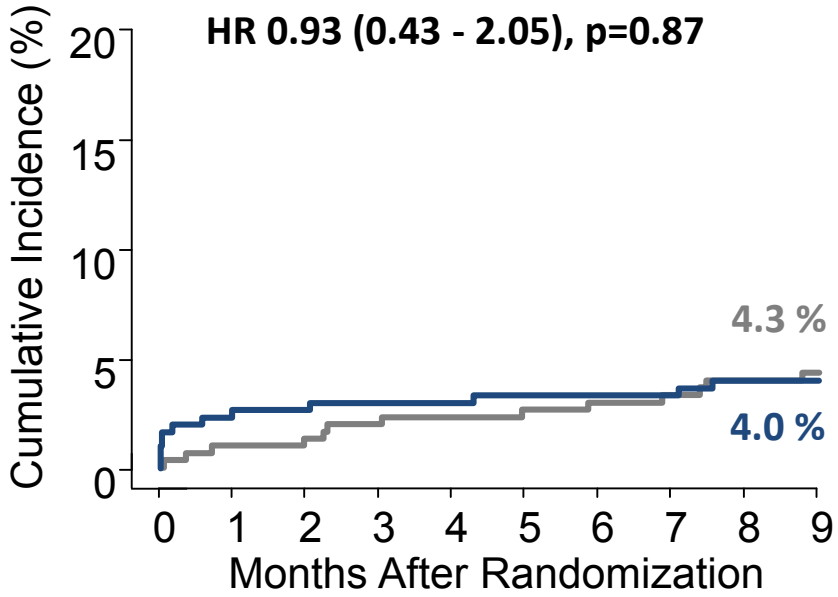
DES = Drug-eluting stent; BMS = Bare-metal stent; BVS = Bioresorbable vascular scaffold; DEB = Drug-eluting balloon; *One patient had 1 DES and 1 BMS and 1 patient had 1 BMS only. ** These patients were treated with drug eluting balloons (DEB) except for 1 patient in the 6-week group and 1 patient in the 6-month group.

Primary Endpoint

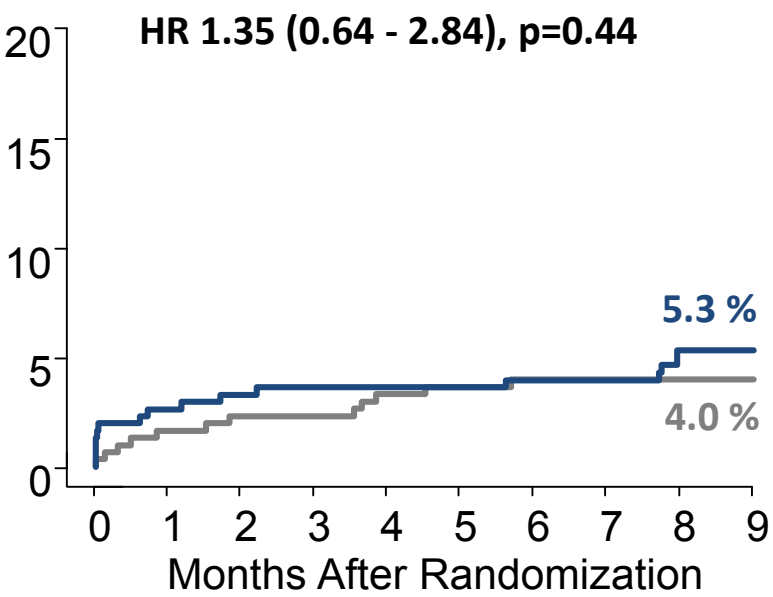


Secondary Endpoints

Cardiac death, myocardial infarction, stent thrombosis or ischemic stroke



TIMI major bleeding



— 6-month group
— 6-week group

Results

	6-week group (n=307)	6-month group (n=307)	Hazard ratio (95% CI)	p value
Death	12 (4.0)	16 (5.2)	0.75 (0.35 -1.59)	0.45
Cardiac death	5 (1.7)	9 (3.0)	0.56 (0.19 - 1.66)	0.29
Myocardial infarction	6 (2.0)	0	-	0.03
Definite stent thrombosis	2 (0.7)	0	-	0.50
Stroke	4 (1.3)	6 (2.0)	0.67 (0.14 - 2.78)	0.75
Ischemic stroke	3 (1.0)	4 (1.3)	0.75 (0.11 - 4.40)	0.99

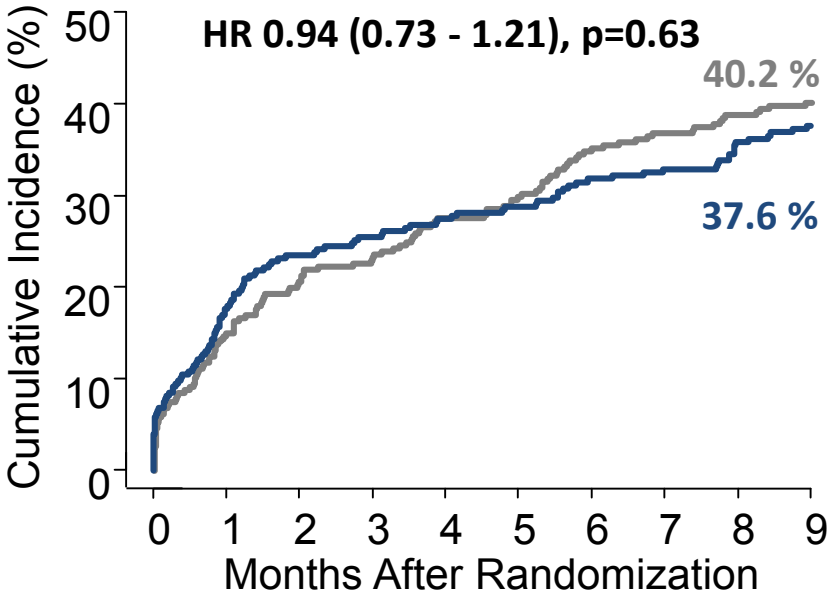
Temporal distribution of MIs in 6-week group:

4 within 24h of PCI
1 at 2.5 weeks } Both groups on triple therapy

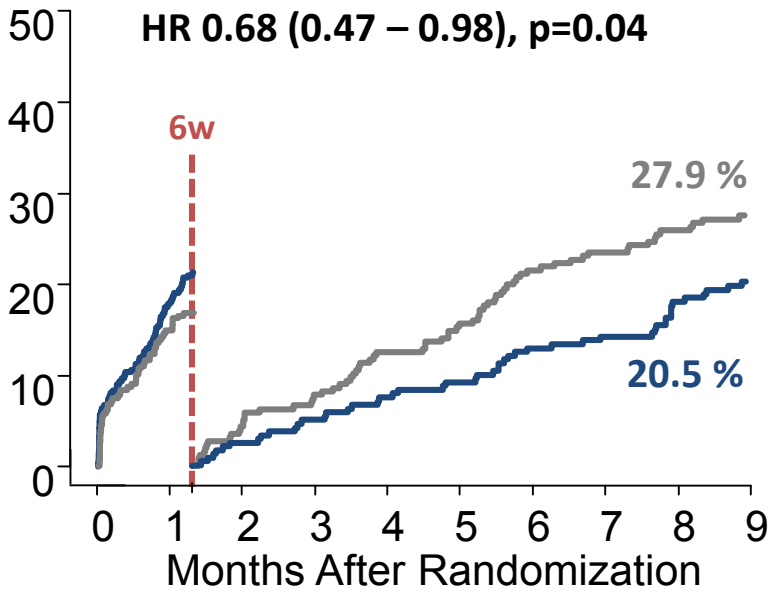
1 at 7 months } Both groups on aspirin and OAC

Any BARC Bleeding (type 1-5)

Any BARC Bleeding



Post-hoc landmark analysis of any BARC Bleeding before and after 6 weeks (6w)



— 6-month group

— 6-week group

Conclusion

- The main finding was that a 6-week triple therapy is not superior to a 6-month triple therapy with regard to net clinical outcomes

- Shortening the duration of triple therapy neither reduced the incidence of major bleeding nor increased the incidence of ischemic events

Conclusion

- **ISAR TRIPLE is the largest randomized trial to date investigating triple therapy after stenting and the first trial evaluating duration of triple therapy**

Thank You For Your Attention