Six Versus Twelve Months of Clopidogrel Therapy After Drug-Eluting Stenting

– the Randomized, Double-Blind, Placebo-Controlled ISAR-SAFE Trial

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Background

- The optimal duration of clopidogrel treatment as part of dual-antiplatelet therapy after drug-eluting stent (DES) implantation remains unclear

Design

- Investigator-initiated, international, multicenter, randomized, double-blind, placebo-controlled trial
- Recruitment period: October 2008 - April 2014

Hypothesis

In patients with DES implantation, 6 months of clopidogrel is non-inferior to 12 months in terms of clinical outcomes

Eligibility Criteria

Major Inclusion Criteria:

- Patients on clopidogrel therapy at 6 (-1/+2) months after DES implantation
- Written informed consent

Major Exclusion Criteria:

- Age ≤18 years
- Clinically symptoms or signs of ischemia and/or angiographic lesions requiring revascularization
- Previous stent thrombosis
- DES in left main coronary artery at index intervention
- STEMI and NSTEMI during the last 6 months after DES implantation
- Malignancies or other comorbid conditions with a life expectancy <1 year or that may result in protocol noncompliance
- Planned major surgery within the next 6 months with the need to discontinue antiplatelet therapy
- Active bleeding; bleeding diathesis; history of intracranial bleeding
- Oral anticoagulation
- Known allergy or intolerance to aspirin or clopidogrel

Endpoints

- **Primary endpoint:**

  Composite of death, myocardial infarction, stent thrombosis, stroke and TIMI major bleeding at 9 months after randomization

- **Secondary endpoints:**

  Individual components of the primary endpoint

40 Recruiting Centers Worlwide – 20 Highest Enrolling Centers

- Deutsches Herzzentrum München, TU, Munich, Germany
- Klinikum rechts der Isar, Munich, Germany
- Herzzentrum Bad Krozingen, Germany
- St. Antonius Hospital, Nieuwegein, Netherlands
- Shenyang Northern Hospital, China
- Leuven University Hospital, Belgium
- Herzzentrum Bad Segeberg, Germany
- Helios Klinikum Wuppertal, Witten/ Herdecke University, Germany
- Aarhus University Hospital, Denmark
- Krankenhaus Landshut-Achdorf, Germany
- University Hospital Göttingen, Germany
- Städt. Klinikum Neuperlach, Germany
- Herzzentrum Lahr/Baden, Germany
- Ulm University Hospital, Germany
- Regensburg University Hospital, Germany
- Klinikum Garmisch-Partenkirchen, Germany
- Städt. Klinikum Bogenhausen, Munich, Germany
- Rostock University Hospital, Germany
- Regensburg Barmherzige Brüder, Germany
- Isala Klinieken Zwolle, Netherlands

Study Organisation

Steering Committee:

Adnan Kastrati (Chair)

Julinda Mehilli (Coordinating Investigator)

Jurrien M ten Berg (PI)

Josef Dirschinger (PI)

DSMB:

Johannes Mann

Franz Hofmann

Dieter Hauschke

Coordinating Center:

ISAResearch Center Munich

Event Adjudication Committee:

Claus Schmitt (Chairman)

Dritan Poci

Petra Barthel

Nicolaus Sarafoff

Andreas Stein

Gjin Ndrepepa

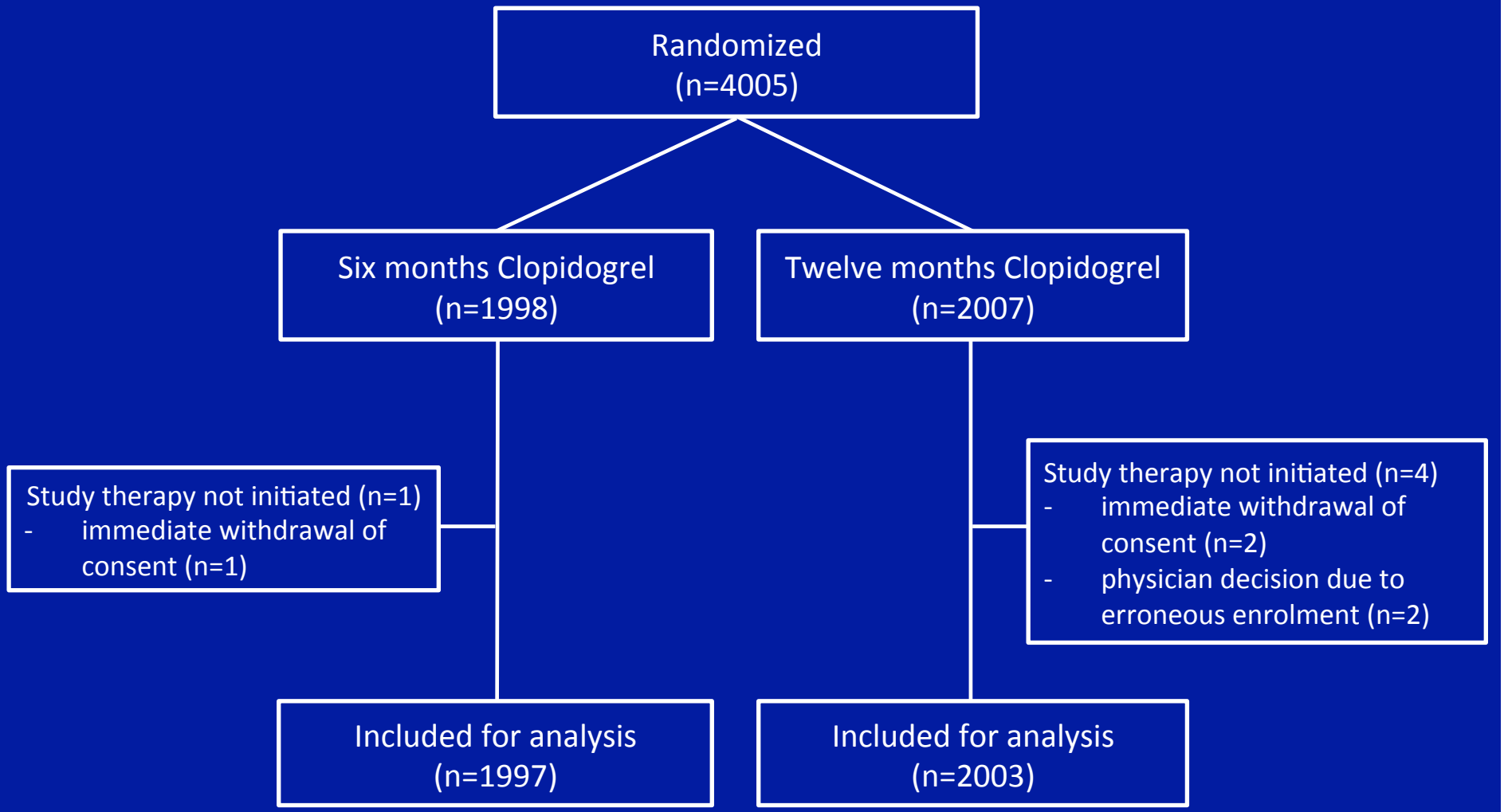
Sample Size Calculation

- Assumptions:
  - Incidence of the primary endpoint in the 12 month clopidogrel group: 10%
  - Margin of non-inferiority: 2% (absolute)
  - Power 80%
  - 1-sided α-Level 0.05

→ Enrolment of 6,000 patients required

- A blinded analysis showed lower than expected overall event rates. This, along with slow recruitment, induced the DSMB and the Steering Committee to recommend termination of recruitment at a sample size of 4000 patients

Study Flow


Randomized
(n=4005)
Six months Clopidogrel
(n=1998)
Twelve months Clopidogrel
(n=2007)
Study therapy not initiated (n=1)
- immediate withdrawal of consent (n=1)
Study therapy not initiated (n=4)
- immediate withdrawal of consent (n=2)
- physician decision due to erroneous enrolment (n=2)
Included for analysis
(n=1997)
Included for analysis
(n=2003)

Baseline Characteristics

	Six months Clopidogrel (n=1997)	Twelve months Clopidogrel (n=2003)
Age, years	67.2 [59.3-73.3]	67.2 [59.1-73.7]
Women	386/1997 (19.3)	391/2003 (19.5)
Arterial hypertension	1797/1994 (90.1)	1830/2001(91.5)
Hypercholesterolemia	1747/1996 (87.5)	1748/2001 (87.4)
Diabetes mellitus	495/1996 (24.8)	484/2001 (24.2)
Family history of premature CAD	707/1935 (36.5)	680/1907 (35.7)
Active Smoker	292/1996 (14.6)	306/1999 (15.3)
Prior myocardial infarction	516/1995 (25.9)	491/2001 (24.5)
Prior CABG	152/1970 (7.7)	149/1976 (7.5)
Body mass index, kg/m^2	27.2 [24.9-30.1]	27.5 [24.9-30.4]

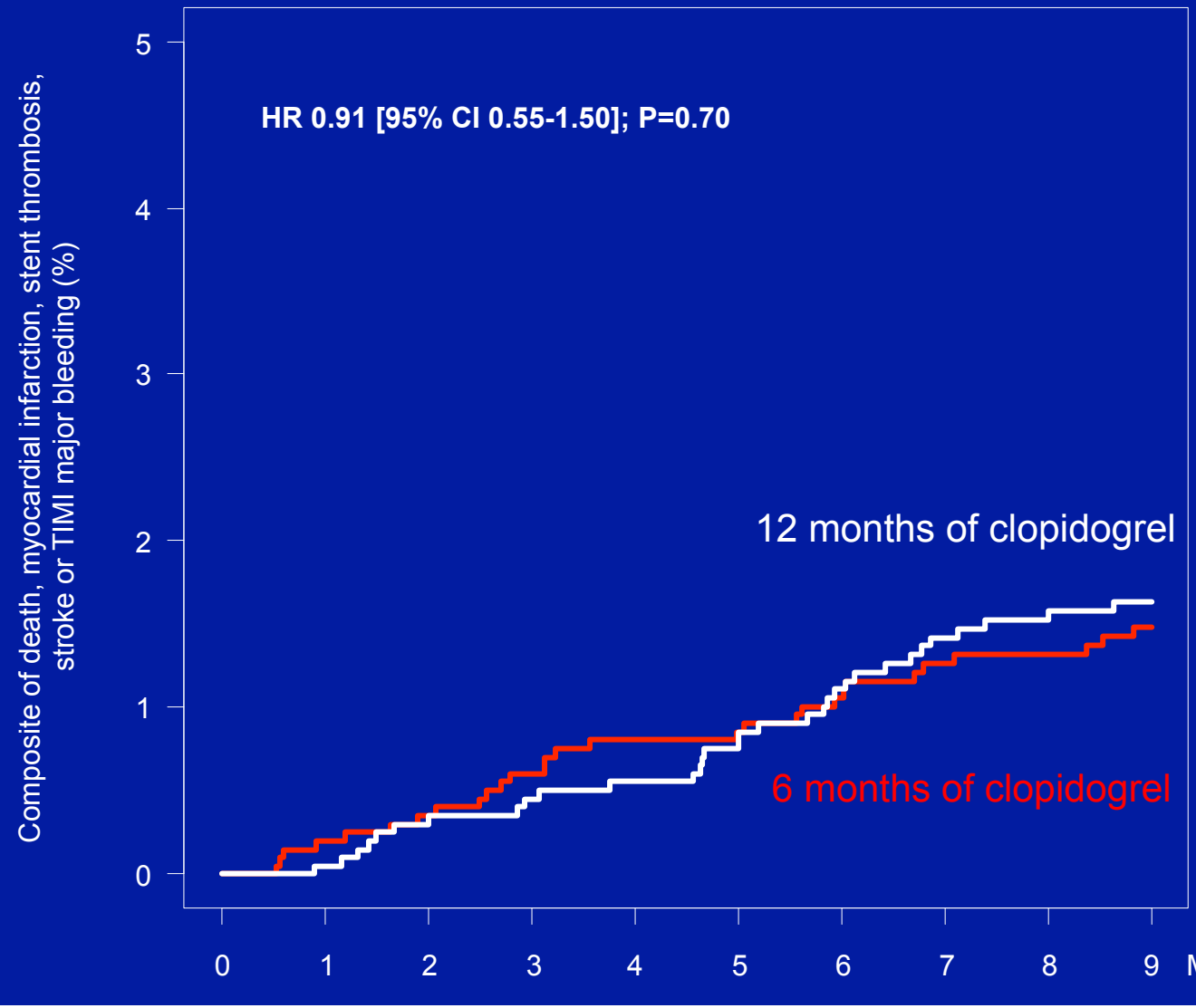
Angiographic and Procedural Characteristics (1/2)

	Six months Clopidogrel (n=1997)	Twelve months Clopidogrel (n=2003)
Clinical Presentation		
- Stable CAD	969/1994 (48.6)	956/2001 (47.8)
- NSTE-ACS	636/1994 (31.9)	641/2001 (32.0)
- STEMI	158/1994 (7.9)	166/2001 (8.3)
- Silent Ischemia	218/1994 (10.9)	227/2001 (11.3)
- Arrhythmia	13/1994 (0.7)	11/2001 (0.6)
Reduced LVEF	476/1850 (25.7)	505/1876 (26.9)
Multivessel Disease	1224/1996 (61.3)	1237/2002 (61.8)
Target Vessel		
- LAD	794/1997 (39.8)	812/2003 (40.6)
- LCx	528/1997 (26.4)	480/2003 (24.0)
- RCA	636/1997 (31.8)	682/2003 (34.0)
- Left Main	9/1997 (0.5)	3/2003 (0.2)
- Bypass Graft	30/1997 (1.5)	26/2003 (1.3)
Lesion characteristics		
- Complex lesion	837/1977 (42.3)	903/1984 (45.5)
- Chronic total occlusion	155/1995 (7.8)	148/1998 (7.4)
- Bifurcation lesion	384/1994 (19.3)	383/1998 (19.2)

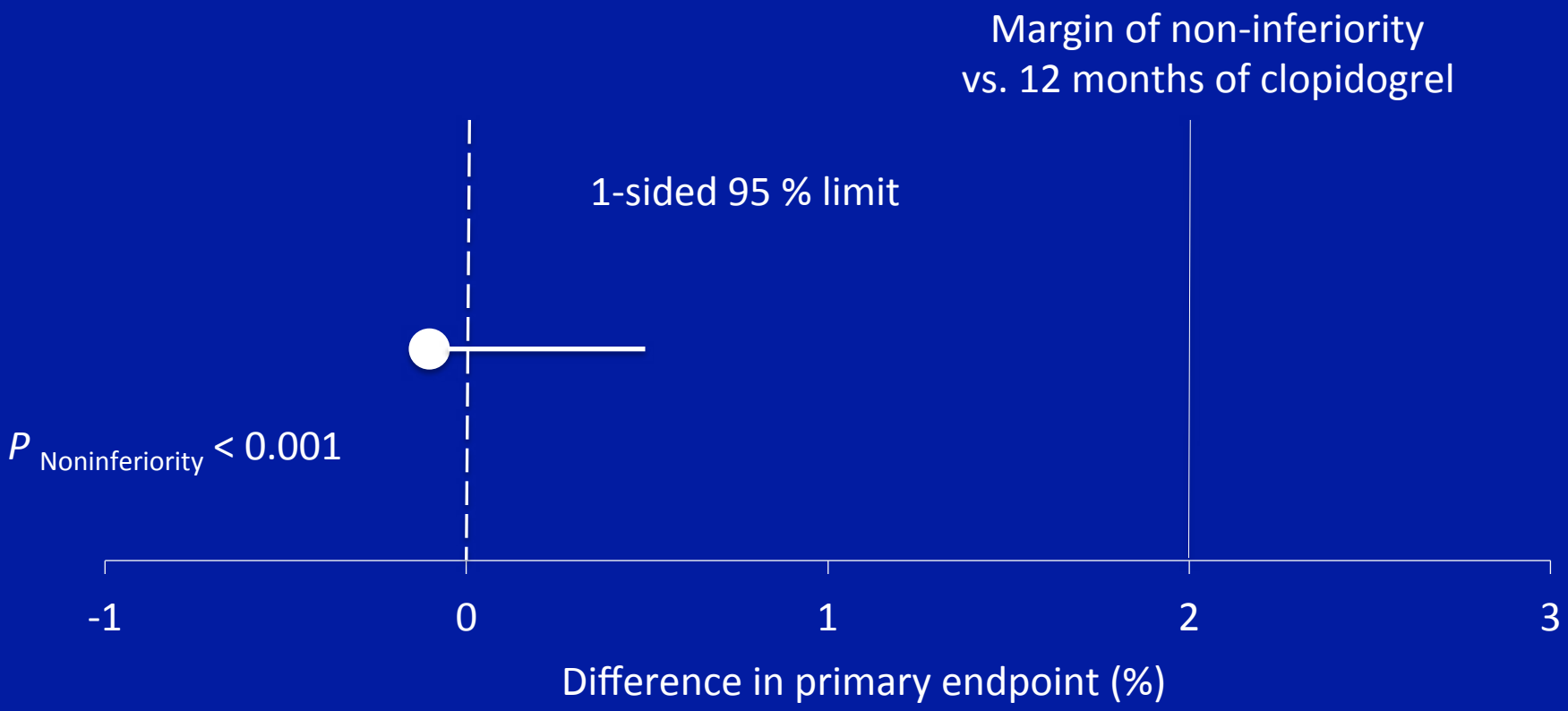
Angiographic and Procedural Characteristics (2/2)

	Six months Clopidogrel (n=1997)	Twelve months Clopidogrel (n=2003)
Vessel size, mm	3.00 [2.75-3.50]	3.00 [2.75-3.50]
Multilesion intervention	749/1997 (37.5)	754/2003 (37.6)
Drug-eluting stent type		
- Early gen. PES	44/1996 (2.2)	46/2003 (2.3)
- Early gen. SES	176/1996 (8.8)	156/2003 (7.8)
- New gen. SES	323/1996 (16.2)	326/2003 (16.3)
- Everolimus-eluting stent	948/1996 (47.5)	988/2003 (49.3)
- Zotarolimus-eluting stent	312/1996 (15.6)	294/2003 (14.7)
- Biolimus-eluting stent	165/1996 (8.3)	171/2003 (8.5)
- Bioresorbable EES	10/1996 (0.5)	5/2003 (0.3)
- Bare metal stent	8/1996 (0.4)	6/2003 (0.3)
- Drug-coated balloon	8/1996 (0.4)	9/2003 (0.4)
- Plain balloon angioplasty	2/1996 (0.1)	2/2003 (0.1)
Number of stents	1.67 ±0.95	1.69 ±0.97
Total stented length, mm	28 [18-43]	28 [18-43]

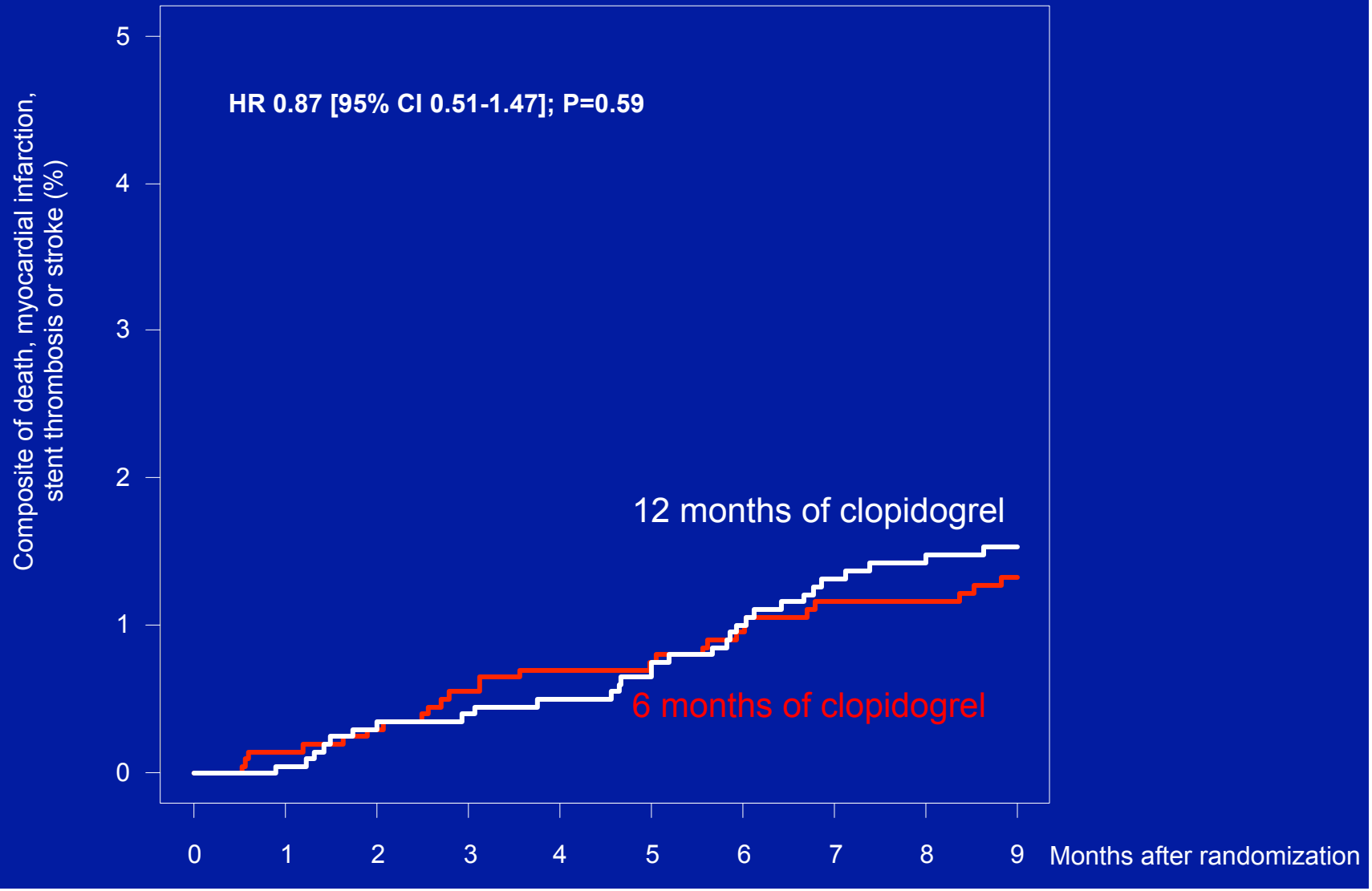
Primary Endpoint



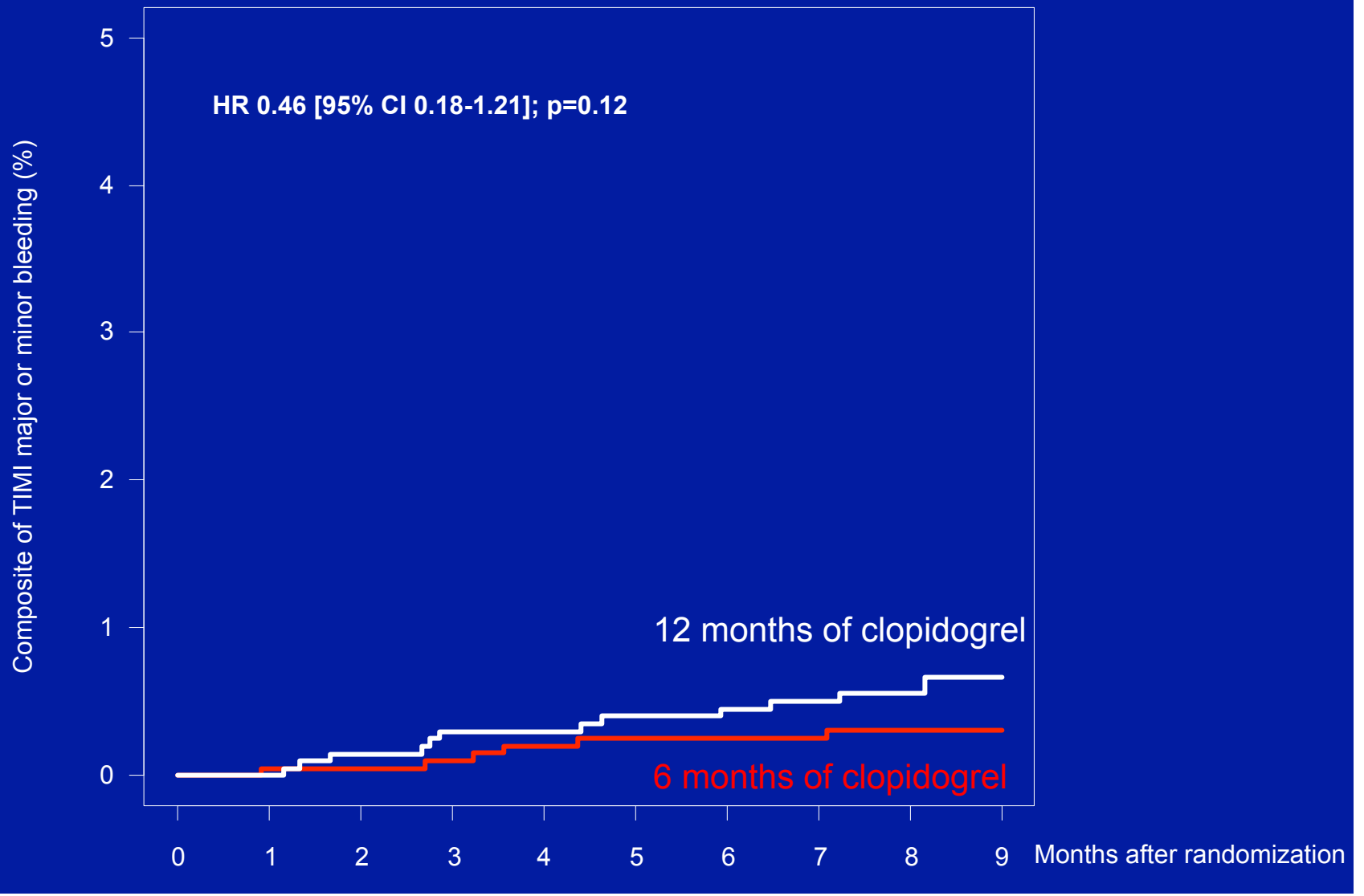
Primary Endpoint



Composite of Death, Myocardial Infarction, Stent thrombosis or Stroke



TIMI Major or Minor Bleeding



Clinical Outcomes

	Six months Clopidogrel (n=1997)	Twelve months Clopidogrel (n=2003)	HR (95% CI)	*P*
Primary endpoint — the composite of death, myocardial infarction, definite or probable stent thrombosis, stroke or TIMI major bleeding)	29 (1.5)	32 (1.6)	0.91 (0.55-1.50)	0.70
Secondary endpoints				
- Death	8 (0.4)	12 (0.6)	0.66 (0.27-1.63)	0.37
- Myocardial infarction	13 (0.7)	14 (0.7)	0.93 (0.44-1.97)	0.85
- Stent thrombosis (def. or prob.)	5 (0.3)	4 (0.2)	1.25 (0.33-4.65)	0.74
- Stroke	7 (0.4)	5 (0.3)	1.40 (0.44-4.41)	0.57
- TIMI major Bleeding	4 (0.2)	5 (0.3)	0.80 (0.21-2.98)	0.74

Clinical Outcomes

	Six months Clopidogrel (n=1997)	Twelve months Clopidogrel (n=2003)	HR (95% CI)	*P*
Composite of death, myocardial infarction, definite or probable stent thrombosis or stroke	26 (1.3)	30 (1.5)	0.87 (0.51-1.47)	0.59
Definite stent thrombosis	5 (0.3)	3 (0.2)	1.66 (0.40-6.96)	0.49
TIMI minor bleeding	2 (0.1)	8 (0.4)	0.25 (0.05-1.17)	0.08
TIMI major or minor bleeding	6 (0.3)	13 (0.7)	0.46 (0.18-1.21)	0.12

Summary And Conclusion

- After DES implantation, 6 months of clopidogrel therapy is non-inferior to 12 months of clopidogrel regarding net clinical outcome

- The results of the trial must be considered in view of its premature termination and lower than expected event rates