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FASTTRACK CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 versus 12 months of clopidogrel therapy after drug-eluting stenting

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Background In patients receiving aspirin, the optimal duration of clopidogrel therapy after drug-eluting stent (DES) implantation remains unclear.

Methods This multicentre, randomized, double-blind, placebo-controlled trial tested the hypothesis that in patients undergoing DES implantation, 6 months of clopidogrel is non-inferior to 12 months in terms of clinical outcomes. At 6 months after DES implantation, patients on clopidogrel were randomly assigned to either a 6-month period of placebo or an additional 6-month period of clopidogrel. The primary endpoint was the composite of death, myocardial infarction, stent thrombosis, stroke, and thrombolysis in myocardial infarction major bleeding at 9 months after randomization.

Results Owing to slow recruitment and low event rates, the trial was stopped prematurely after enrolment of 4005 of 6000 planned patients. Of 4000 patients included in the final analysis, 1997 received 6 months of clopidogrel and 2003 received 12 months. The primary endpoint occurred in 29 patients (1.5%) assigned to 6 months of clopidogrel and 32 patients (1.6%) assigned to 12 months, observed difference −0.1%, upper limit of one-sided 95% confidence interval (CI) 0.5%, limit of non-inferiority 2%, $P_{\text{for noninferiority}} < 0.001$. Stent thrombosis was observed in five patients (0.3%) assigned to 6 months of clopidogrel and three patients (0.2%) assigned to 12 months; hazard ratio (HR) 1.66, 95% CI: 0.40–6.96,

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$P = 0.49$. Thrombolysis in myocardial infarction major bleeding was observed in 4 patients (0.2%) assigned to 6 months clopidogrel and 5 patients (0.3%) assigned to 12 months; HR 0.80, 95% CI: 0.21–2.98, $P = 0.74$.

Conclusions In the present trial, characterized by low event rates, we did not observe a significant difference in net clinical outcome between 6 and 12 months of clopidogrel therapy after DES implantation. However, the results of the trial must be considered in view of its premature termination and lower than expected event rates.

The trial is registered with ClinicalTrials.gov, Identifier: NCT00661206.

Keywords Clopidogrel • Double-blind • Dual antiplatelet therapy • Drug-eluting stent • Randomized trial • Stent thrombosis

Background

Patients undergoing percutaneous coronary intervention (PCI) with stent implantation require dual antiplatelet therapy (DAPT) with acetylsalicylic acid indefinitely and an ADP-receptor antagonist for a prescribed period.[1] The introduction of drug-eluting stents (DES) for coronary intervention has resulted in improvement in overall clinical outcomes compared with treatment with bare metal stents.[2,3] However concern exists regarding a small but significant increase in the incidence of stent thrombosis late after intervention with DES.[4,5] To mitigate this risk general consensus exists that patients treated with DES require a longer duration of DAPT, though the optimal duration of clopidogrel therapy in this setting remains poorly defined.

Uncertainty with regard to the recommended duration of clopidogrel after DES implantation is also reflected in differing guideline recommendations in Europe and the USA. While in patients with stable coronary artery disease a course of 6 months of clopidogrel is considered sufficient according to the European Guidelines,[6] at least 12 months of clopidogrel is recommended by US Guidelines.[7] In recent years a number of clinical trials have examined the issue of DAPT duration after DES implantation.[8–13] These trials differed in the durations of clopidogrel in the study and control groups—ranging from 3 to 12 months vs. 12–24 months, respectively. On the other hand a common feature of all trials was the absence of a double-blind design. A meta-analysis of randomized trial data showed no advantage of longer duration DAPT in terms of reducing ischaemic endpoints but a clear signal for an increased bleeding risk with DAPT extension[14] and a recent randomized trial reported similar findings when therapy duration was extended beyond 12 months.[15]

We designed a multicentre, randomized, double-blind, placebo-controlled trial in order to assess whether in patients with DES implantation 6 months of DAPT are non-inferior to 12 months of DAPT in terms of clinical outcome.

Methods

Study design

ISAR-SAFE is an investigator-initiated, international, multicentre, randomized, double-blind, placebo-controlled trial. The authors are solely responsible for the design, conduct, data analyses as well as drafting and editing of the manuscript and its final content. Full details of the trial rationale and design have previously been published.[16]

Patient population

Patients were recruited at 40 study centres worldwide. A list of participating centres and investigators is provided in the Supplementary material online, Appendix. We included patients with written informed consent that were receiving clopidogrel therapy at 6 (−1/+2) months after DES implantation due to symptoms or signs of coronary artery disease, i.e. even patients with acute coronary syndrome (ACS) at the index-PCI. Major exclusion criteria were age ≤18 years, patients with clinical symptoms or proof of ischaemia and/or angiographic lesions requiring revascularization, previous stent thrombosis, DES implantation in the left main coronary artery, myocardial infarction during the 6 months after DES implantation, malignancies or other comorbid conditions with a life-expectancy of <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 and known allergy or intolerance of the study medication. The study was approved by the Ethics Committee of each participating centre.

Randomization

Patients meeting the eligibility criteria were randomly assigned in a 1:1 ratio to either a 6-month period of placebo (total length of clopidogrel therapy after DES implantation: 6 months) or to an additional 6-month period of clopidogrel (total length of clopidogrel therapy after DES implantation: 12 months). Sealed opaque envelopes containing a computer-generated sequence with randomly permuted block lengths were used. Separate block randomization was performed for each participating centre.

Study treatment

At 6 months after PCI, study participants received further 6 months of either identical appearing tablets of placebo or 75 mg clopidogrel (Plavix©). After 6 months, study medication was stopped and it was not recommended to start with open-label clopidogrel again. Concomitant medication consisted of 81–200 mg of acetylsalicylic acid. Other medication was prescribed at the discretion of the treating physician.

Follow-up

All the patients were scheduled to undergo clinical follow-up at 30 days, 6, and 9 months after randomization by telephone, letter, or office visit. At any follow-up time point, patients were asked about the occurrence of adverse events and their compliance to the study medication.

Endpoints and definitions

The primary endpoint is the composite of death, myocardial infarction, stent thrombosis (definite or probable), stroke, or thrombolysis in myocardial infarction (TIMI) major bleeding at 9 months after randomization, i.e. 15 months after the index intervention.

The reason for choosing 9 months and not 6 months after randomization for the evaluation of the primary endpoint were concerns about the potential existence of a rebound phenomenon after clopidogrel discontinuation, which could have created an imbalance in favour of the 12-month clopidogrel group.

Secondary endpoints are the individual components of the primary endpoint. The definitions of death and stent thrombosis were based on the recommendations of the Academic Research Consortium (ARC).[17] The definition of myocardial infarction and major bleeding was adapted from the TIMI study group. Thrombolysis in myocardial infarction major bleeding was defined as intracranial bleeding or clinically significant overt sign of haemorrhage associated with a drop in haemoglobin of $\geq$50 g/L (or an absolute drop in haematocrit of at least 15% when haemoglobin was not available). Acute coronary syndrome was defined as unstable angina (troponin-negative), non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction.

The diagnosis of stroke required confirmation by computed tomography, magnetic resonance imaging, or pathological confirmation. A detailed description of the endpoint definitions has previously been published.[16] Bleeding events were also classified according to the Bleeding Academic Research Consortium (BARC) criteria.[18] All events were adjudicated and classified by an event adjudication committee whose members were unaware of the assigned treatment.

Data management and monitoring

Data were collected and analysed at the ISAResearch Center in Munich, Germany. Monitoring was performed for German, Danish, and Swiss sites which together contributed 77% of the enrolled patients (63% of the study centres). The trial was monitored by the Münchner Studienzentrum in Germany, Qmed Consulting ApS in Denmark and Renate Schick (Freelancer) in Switzerland.

Statistical considerations

The trial was designed to test the hypothesis that a 6-month duration of clopidogrel therapy after DES implantation is non-inferior to a 12-month therapy duration in terms of clinical outcome. Sample size calculation was based on the following assumptions: incidence of the primary end-point of 10% in both groups (estimated difference 0%),[19] margin of non-inferiority of +2% (relative +20%), power of 80%, and a one-sided α-level of 0.05. Thus, the 6-month group would be considered non-inferior to the 12-month group if the upper 95% CI of the difference in the incidence of the primary endpoint does not exceed the pre-specified 2% limit. This relative 20% limit of non-inferiority was chosen under the consideration that any difference above this limit would be clinically relevant. With these assumptions, enrolment of 2800 patients per group was required. To compensate for potential losses to follow-up, it was planned to enrol a total of 6000 patients. Sample size calculation was performed with nQuery Advisor (Statistical Solutions, Cork, Ireland).

A protocol amendment before the completion of the study required an interims analysis after enrolment of two-thirds of the patients. The blinded analysis showed lower than expected overall event rates. This finding—along with slow recruitment—induced the Data Safety Monitoring Board and Steering Committee to recommend termination of recruitment at a sample size of 4000 patients.

Categorical variables were summarized using frequencies and proportions and compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous data were summarized using mean $\pm$ standard deviation or median (25th, 75th percentiles) and compared using Student's *t*-test or non-parametric Wilcoxon rank-sum test, respectively.

The main analysis was performed by testing for non-inferiority of 6 months clopidogrel in terms of the primary endpoint at 9 months after randomization, i.e. 15 months after DES implantation. The test was one-sided and an alpha level of 0.05 was considered statistically significant. Non-inferiority testing was performed with EquivTest, version 1.0 (from Statistical solutions). The CI was calculated based on the method of Hauck and Anderson.[20]

After non-inferiority testing, all subsequent comparisons were done with superiority testing and a two-sided alpha level of 0.05 [using the software R (version 2.15.2), The R Foundation for Statistical Computing]. Cumulative event rates were calculated by the use of the Kaplan–Meier method and a Cox proportional hazards model was used for the comparison of the two study groups. The primary end-point was also assessed in pre-specified subgroups defined by age, gender, presence of diabetes mellitus, clinical presentation with ACS at the time of DES implantation, complexity of the treated lesion and left ventricular function. All analyses were performed in a blinded manner regarding the randomly assigned treatment. Unblinding of the study groups was done after completion of the statistical analyses regarding the primary and secondary endpoints.

Results

Patients and procedures

Between October 2008 and April 2014, a total of 4005 patients were enrolled in the trial, 1998 patients were randomly assigned to 6 months of clopidogrel and 2007 patients to 12 months. *Figure 1* summarizes the study flow. Five patients (1 assigned to 6 months of clopidogrel and 4 assigned to 12 months of clopidogrel) withdrew their consent immediately or were excluded by the treating physician before taking any study medication and were not included in the final analysis.

Table 1 summarizes the baseline clinical and demographic characteristics according to treatment allocation to 6 months of clopidogrel or 12 months. Angiographic and procedural characteristics at the time of index intervention are shown in *Table 2*. Overall 1601 patients (40%) presented with an ACS at the index intervention. *Table 3* shows the medication patients were receiving at the time of randomization.

Premature discontinuation of the study drug was recorded in 12.7% of the patients assigned to 6 months of clopidogrel and 13.9% of the patients assigned to 12 months of clopidogrel ($P = 0.24$).

Clinical outcomes

Thirty-seven patients (14 assigned to 6 months of clopidogrel and 23 assigned to 12 months) withdrew their consent for continued study participation after initiation of the study drug with agreement to the use of their data up to the time point of withdrawal. The median time interval to withdrawal was 105 (IQR 26–270) days.

Clinical follow-up at 9 months was available for all but 262 patients, 127 assigned to 6 months of clopidogrel (6.4%) and 135 patients (6.9%) assigned to 12 months of clopidogrel; $P = 0.59$. In patients within incomplete 9-month follow-up, the median duration of follow-up was 199 (IQR 181–231) days. A total of 55 patients (1.4%), 30 patients assigned to 6 months of clopidogrel and 25

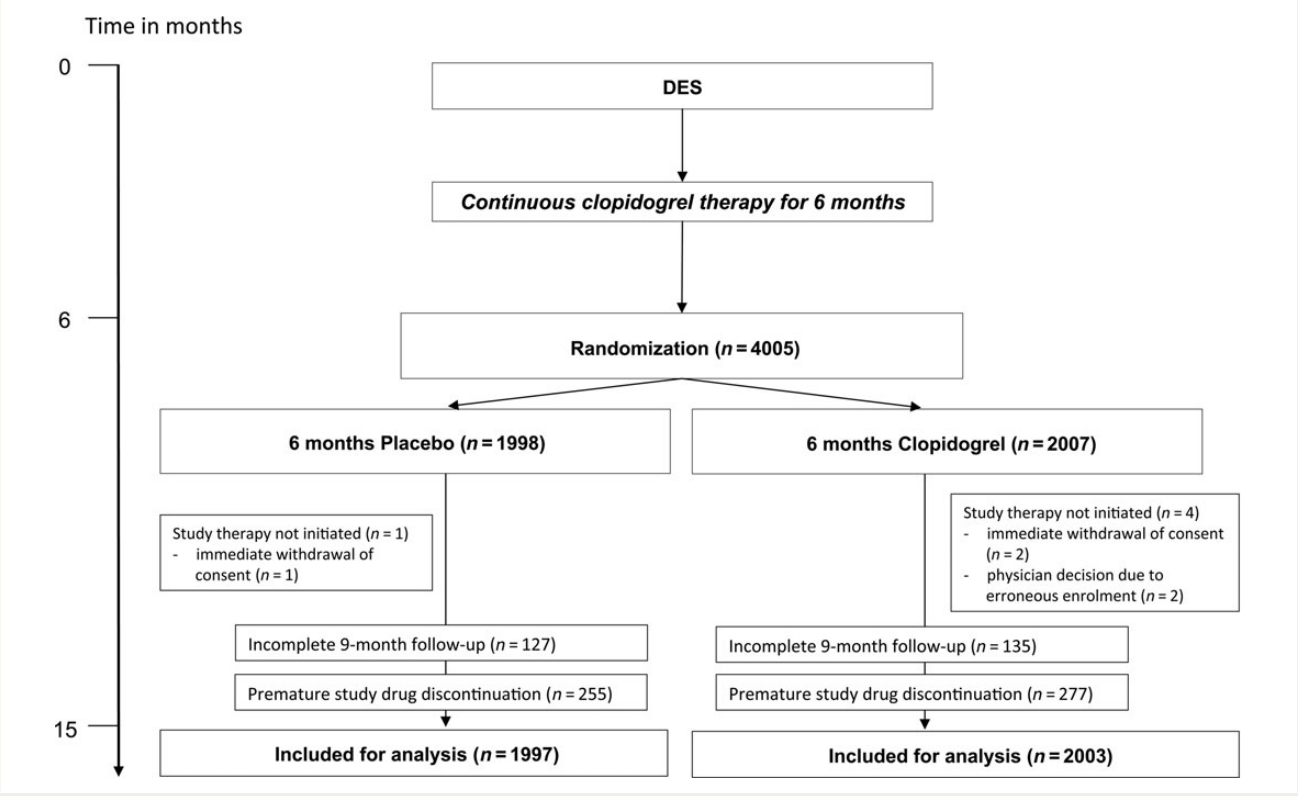

Figure 1 Study flow diagram.

Table 1 Baseline clinical and demographic characteristics at the time of randomization

	Six months clopidogrel (*n* = 1997)	Twelve months clopidogrel (*n* = 2003)
Age, years	67.2 (59.3–73.3)	67.2 (59.1–73.7)
Female	386/1997 (19.3)	391/2003 (19.5)
Arterial hypertension	1797/1994 (90.1)	1830/2001(91.5)
Hypercholesterolaemia	1747/1996 (87.5)	1748/2001 (87.4)
Diabetes mellitus	495/1996 (24.8)	484/2001 (24.2)
Insulin requiring	158/1996 (7.9)	157/2001 (7.8)
Family history	707/1935 (36.5)	680/1907 (35.7)
Smoking status		
Active smoker	292/1996 (14.6)	306/1999 (15.3)
Former smoker	703/1996 (35.2)	719/1999 (36.0)
History of prior myocardial infarction	516/1995 (25.9)	491/2001 (24.5)
History of prior coronary artery bypass graft	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)

Data are shown as number (percentage) or median (inter-quartile range).

patients assigned to 12 months of clopidogrel, had a follow-up shorter than 6 months ($P = 0.51$).

Clinical outcomes according to the study group are reported in *Table 4*. Overall, the incidence of events was lower than expected. At 9 months, the composite primary endpoint of death, myocardial infarction, stent thrombosis, stroke, or major bleeding was observed in 29 patients (1.5%) assigned to 6 months of clopidogrel and 32 patients (1.6%) assigned to 12 months of clopidogrel (observed difference −0.1%, upper limit of one-sided 95% confidence interval (CI) 0.5%; upper limit of one-sided 97.5% CI 0.6%; $P_{\text{noninferiority}} < 0.001$, HR 0.91, 95% CI: 0.55–1.50, $P_{\text{for superiority}} = 0.70$ (graphical representation of primary endpoint shown in *Figure 2*). Regarding the secondary endpoints, 8 patients (0.4%) assigned to 6 months of clopidogrel and 12 patients (0.6%) assigned to 12 months of clopidogrel died within 9 months; HR 0.66, 95% CI: 0.27–1.63, $P = 0.37$. There were 8 cases of definite stent thrombosis, 5 (0.3%) in patients assigned to 6 months of clopidogrel and 3 (0.2%) in patients assigned to 12 months of clopidogrel (HR 1.66, 95% CI: 0.40–6.96, $P = 0.49$). The rates of myocardial infarction and stroke were low and comparable in both study groups [myocardial infarction: 13 patients (0.7%) vs. 14 patients (0.7%); HR 0.93, 95% CI: 0.44–1.97, $P = 0.85$ and stroke: 7 patients (0.4%) vs. 5 (0.3%); HR 1.40, 95% CI 0.44–4.41, $P = 0.57$. The composite of death, myocardial infarction, stent thrombosis, or stroke is shown in *Figure 3*.

Table 2 Angiographic and procedural characteristics at the time of index intervention

	Six months clopidogrel ($n = 1997$)	Twelve months clopidogrel ($n = 2003$)
Clinical presentation		
Stable angina	969/1994 (48.6)	956/2001 (47.8)
Unstable Angina	429/1994 (21.5)	438/2001 (21.9)
Non-ST-segment elevation myocardial infarction	207/1994 (10.4)	203/2001 (10.1)
ST-segment elevation myocardial infarction	158/1994 (7.9)	166/2001 (8.3)
Silent ischaemia	218/1994 (10.9)	227/2001 (11.3)
Arrhythmia	13/1994 (0.7)	11/2001 (0.6)
Reduced left ventricular- ejection fraction (<55%)	476/1850 (25.7)	505/1876 (26.9)
Number of diseased vessels		
1	772/1996 (38.7)	765/2002 (38.2)
2	609/1996 (30.5)	616/2002 (30.8)
3	615/1996 (30.8)	621/2002 (31.0)
Multivessel disease	1224/1996 (61.3)	1237/2002 (61.8)
Target vessel		
Left anterior descending coronary artery	794/1997 (39.8)	812/2003 (40.6)
Left circumflex coronary artery	528/1997 (26.4)	480/2003 (24.0)
Right coronary artery	636/1997 (31.8)	682/2003 (34.0)
Left main coronary artery	9/1997 (0.5)	3/2003 (0.2)
Bypass graft	30/1997 (1.5)	26/2003 (1.3)
Lesion characteristics		
Complex lesion[a]	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)
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 generation paclitaxel-eluting stent	44/1996 (2.2)	46/2003 (2.3)
Early generation sirolimus-eluting stent	176/1996 (8.8)	156/2003 (7.8)
New generation sirolimus-eluting stent	323/1996 (16.2)	326/2003 (16.3)
Everolimus-eluting stent	948/1996 (47.5)	988/2003 (49.3)
Zotarolimus-eluting Stent		
Zotarolimus-eluting Endeavor Stent	85/1996 (4.3)	76/2003 (3.8)
Zotarolimus-eluting Resolute Stent	227/1996 (11.4)	218/2003 (10.9)
Biolimus-eluting stent	165/1996 (8.3)	171/2003 (8.5)
Bioresorbable everolimus-eluting stent	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)

Data are shown as number (percentage), mean ± standard deviation or median (inter-quartile range).
[a]Type B2 or C according to the modified American College of Cardiology/American Heart Association classification.

Thrombolysis in myocardial infarction major bleeding was observed in four patients (0.2%) assigned to 6 months of clopidogrel and in five patients (0.3%) assigned to 12 months of clopidogrel, HR 0.80, 95% CI: 0.21–2.98, $P = 0.74$; *Figure 4*. There was a numerically lower rate of TIMI minor bleeding in patients receiving 6 months of clopidogrel [two patients (0.1%) vs. eight patients (0.4%), HR 0.25, 95% CI: 0.05–1.17, $P = 0.08$]. Bleeding according to BARC ≥class 2 was observed in 20 patients (1.0%) assigned to 6 months clopidogrel and 40 patients (2.0%) assigned to 12 months clopidogrel ($P = 0.01$; *Figure 5*).

We specifically looked at the effects of study drug discontinuation in the 12-month group on the occurrence of ischaemic outcomes. At 6 months after randomization, the composite of death, myocardial infarction, stent thrombosis, or stroke was observed in 19/1997 patients (1%) in the 6-month group and 20/2003 patients (1%) in the 12-month group, HR 0.95, 95% CI: 0.51–1.78, $P = 0.88$. From

Table 3 Medication at randomization

	Six months clopidogrel (n = 1997)	Twelve months clopidogrel (n = 2003)
Acetylsalicylic acid	1997/1997 (100)	2002/2003 (99.95)[a]
Beta-blocker	1662/1997 (83.2)	1679/2003 (83.8)
ACE inhibitor[b]	1183/1997 (59.2)	1200/2003 (59.9)
Angiotensin II receptor blocker	450/1996 (22.5)	457/2001 (22.8)
Calcium antagonist	437/1996 (21.9)	445/2003 (22.2)
Diuretic	688/1995 (34.5)	702/2003 (35.0)
Proton pump inhibitor	525/1978 (26.5)	508/1984 (25.6)
Statin	1897/1997 (95.0)	1890/2003 (94.4)

Data are shown as number (percentage).
[a]ACE inhibitor denotes angiotensin-converting enzyme inhibitor.
[b]One patient in the 12 months dual antiplatelet therapy group was not on acetylsalicylic acid but on cilostazol.

Table 4 Clinical outcomes at 9 months

	Six months clopidogrel (n = 1997)	Twelve months clopidogrel (n = 2003)	HR (95% CI)	P-value
Primary endpoint				
The composite of death, myocardial infarction, definite, or probable stent thrombosis, stroke or TIMI[a] major bleeding	29 1.5% (0.9–2.0%)	32 1.6% (1.1–2.2%)		<0.001[#]
Secondary endpoints				
Death	8 0.4% (0.1–0.7%)	12 0.6% (0.3–1%)	0.66 (0.27–1.63)	0.37
Myocardial infarction	13 0.7% (0.3–1.0%)	14 0.7% (0.3–1.1%)	0.93 (0.44–1.97)	0.85
Definite or probable stent thrombosis	5 0.3% (0–0.5%)	4 0.2% (0–0.4%)	1.25 (0.33–4.65)	0.74
Stroke	7 0.4% (0.1–0.6%)	5 0.3% (0–0.5%)	1.40 (0.44–4.41)	0.57
TIMI[a] major Bleeding	4 0.2% (0–0.4%)	5 0.3% (0–0.5%)	0.80 (0.21–2.98)	0.74
Composite of death, myocardial infarction, definite or probable stent thrombosis or stroke)	26 1.3% (0.8–1.8%)	30 1.5% (1.0–2.1%)	0.87 (0.51–1.47)	0.59
Definite stent thrombosis	5 0.3% (0–0.5%)	3 0.2% (0–0.3%)	1.66 (0.40–6.96)	0.49
TIMI[a] minor bleeding	2 0.1% (0–0.2%)	8 0.4% (0.1–0.7%)	0.25 (0.05–1.17)	0.08
TIMI[a] major or minor bleeding	6 0.3% (0.1–0.5%)	13 0.7% (0.3–1.0%)	0.46 (0.18–1.21)	0.12
BARC[b] bleeding	27 1.4% (0.9–1.9%)	55 2.8% (2.1–3.5%)	0.49 (0.31–0.77)	0.002
Class 1	11	20		
Class 2	15	24		
Class 3a	1	11		
Class 3b	4	8		
Class 3c	1	3		
Class 5	0	1		
Blood transfusion	3	9		

Data are shown as numbers and percentages. Percentages and their respective CI correspond to Kaplan–Meier estimates.
[a]TIMI denotes thrombolysis in myocardial infarction, [b]BARC denotes Bleeding Academic Research Consortium [#]P-value from the non-inferiority analysis.

6 to 9 months after randomization, i.e. within 3 months after study drug discontinuation in the 12 month group, 7/1941 patients (0.4%) assigned to 6 months clopidogrel and 10/1945 patients (0.5%) assigned to 12 months clopidogrel suffered from this composite ischaemic outcome, HR 0.70, 95% CI: 0.27–1.83, $P = 0.57$.

Also in patients presenting with an ACS at the index PCI, there was no significant increase in ischaemic events within the 3 months after clopidogrel discontinuation in the 12-month clopidogrel group. From 6 to 9 months after randomization, the composite ischaemic outcome was observed in 5/774 patients (0.7%) assigned to 6 months clopidogrel and 5/777 patients (0.7%) assigned to 12 months clopidogrel, HR 1.0, 95% CI: 0.29–3.44, $P = 0.995$.

Results of the pre-specified and *post hoc* subgroup analysis are shown in *Figure 6*. There was a significant interaction between age

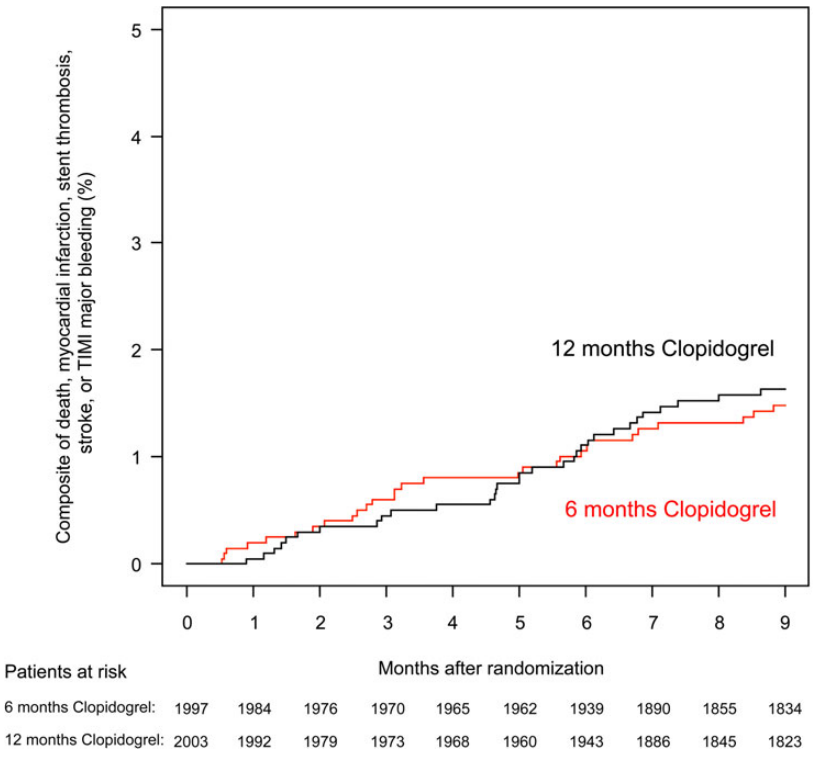

Figure 2 Primary composite endpoint of death, myocardial infarction, stent thrombosis, stroke or thrombolysis in myocardial infarction major bleeding at 9 months in the two study groups of 6 and 12 months clopidogrel therapy.

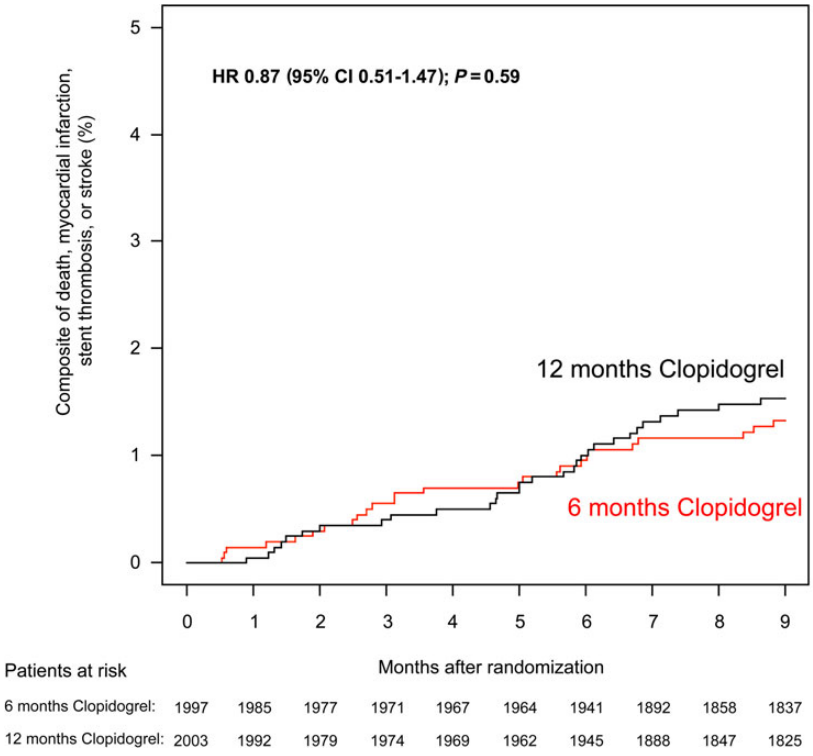

Figure 3 Composite of death, myocardial infarction, stent thrombosis or stroke at 9 months in the two study groups of 6 and 12 months clopidogrel therapy.

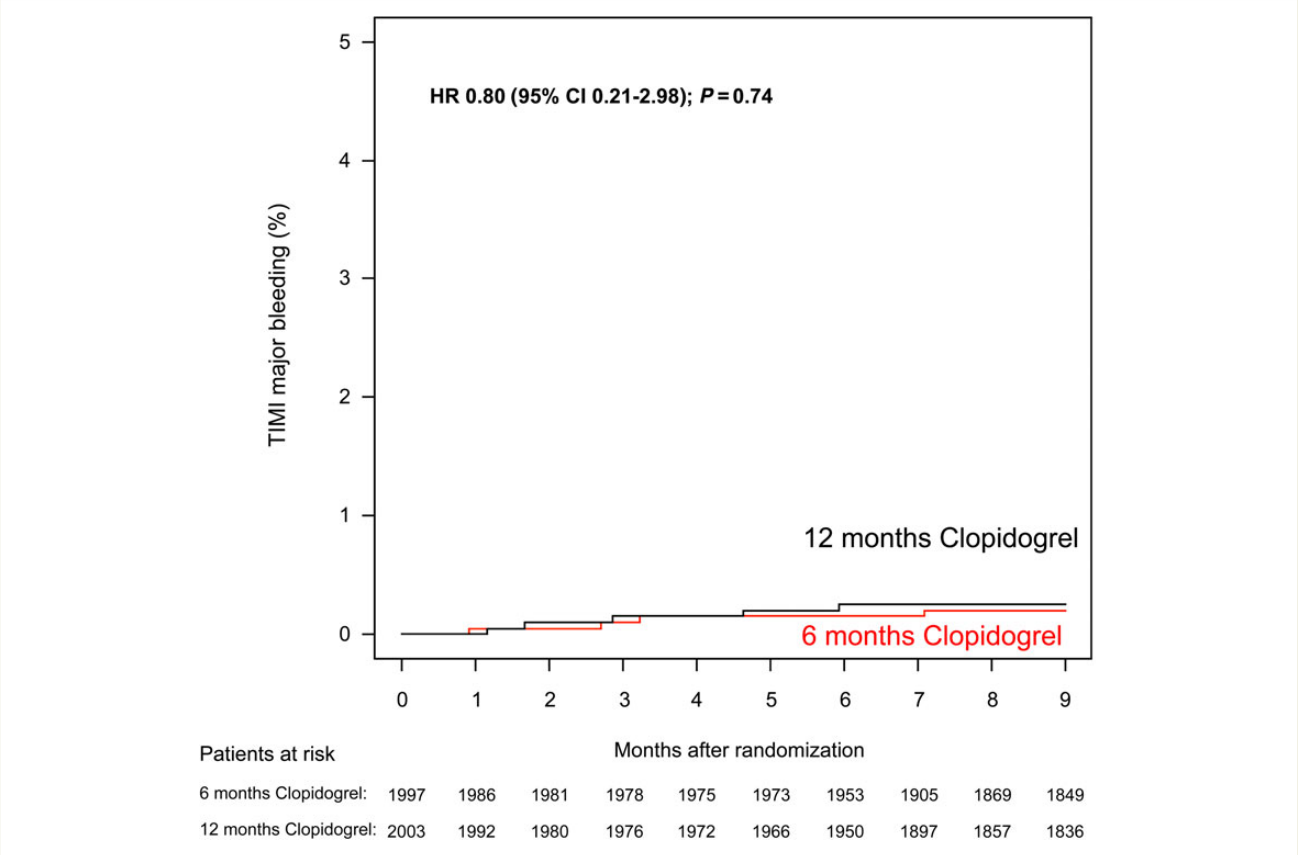

Figure 4 Thrombolysis in myocardial infarction major bleeding at 9 months in the two study groups of 6 and 12 months clopidogrel therapy.

and treatment effect regarding the primary endpoint ($P = 0.03$ for interaction). In patients with an age of 67.2 years or older, the incidence of the primary endpoint tended to be lower with 6 months of clopidogrel, HR 0.60, 95% CI: 0.31–1.13, whereas in patients younger than 67.2 years, there was a trend in favour of 12 months clopidogrel, HR 2.02, 95% CI: 0.81–4.99. Of note, this benefit was driven by ischaemic events. In patients ≥67.2 years, the composite of death, myocardial infarction, stent thrombosis or stroke occurred in 13/999 patients (1.3%) assigned to 6 and 24/1002 patients (2.5%) assigned to 12 months, HR 0.52, 95% CI: 0.27–1.06, whereas in patients <67.2 years, the composite of death, myocardial infarction, stent thrombosis or stroke occurred in 13/998 patients (1.3%) assigned to 6 months clopidogrel and 6/1001 (0.6%) assigned to 12 months clopidogrel, HR 2.18, 95% CI: 0.83–5.74; $P_{\text{for interaction}} = 0.02$). The numerical difference was mostly generated from cases who incurred myocardial infarction or died. Regarding bleeding complications, in patients aged ≥67.2 years TIMI major bleeding was observed in 3/999 patients (0.3%) assigned to 6 months clopidogrel and 3/1002 patients (0.3%) assigned to 12 months clopidogrel, HR 1.0, 95% CI: 0.2–4.9. In patients younger than 67.2 years, 1/998 patients (0.1%) assigned to 6 months clopidogrel and 2/1001 patients (0.2%) assigned to 12 months clopidogrel suffered from TIMI major bleeding, HR 0.50, 95% CI: 0.05–5.53; $P_{\text{for interaction}} = 0.64$).

We also performed *post hoc* subgroup analyses according to stent generation, presence or absence of monitoring, premature discontinuation of study medication, and current smoking. Results are also shown in *Figure 6*.

Discussion

This randomized, double-blind, placebo-controlled trial compared outcomes between patients treated with 6 months vs. 12 months of clopidogrel after DES implantation. The main finding of the ISAR-SAFE trial, characterized by low event rates, was that we did not find a significant difference with 6 months clopidogrel compared with 12 months clopidogrel in terms of net clinical outcome—the composite of death, myocardial infarction, stent thrombosis, stroke, and major bleeding at 9 months after randomization (15 months after DES implantation). However, due to lower than expected event rates and early termination the results of the trial must be interpreted with caution.

In the present trial, the rates of clinical events were significantly lower than those assumed in the study protocol. In fact this has also been a feature of earlier clinical trials examining this issue.[8,21] A number of reasons might be proposed to explain this finding. First, it seems likely that predominantly low-risk patients were included. In contrast to most previous trials on DAPT duration, patients were randomly assigned to treatment strategy at 6 months after DES implantation—i.e. at the time the two treatments actually started to differ—rather than at the time of the index intervention.

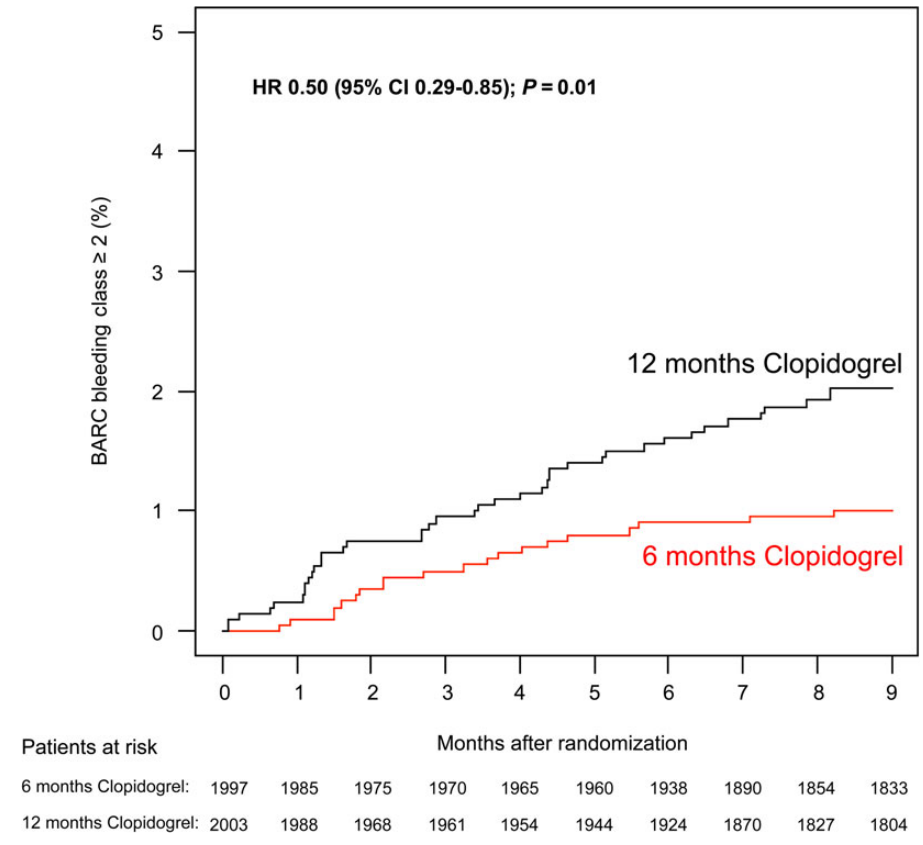

Figure 5 Bleeding class ≥2 According to the Academic Research Consortium Definition at 9 Months in the two study groups of 6 and 12 months clopidogrel therapy.

This method enables optimal assessment of the relative contribution of both treatment durations, as it avoids dilution of treatment effects due to the influence of early events at a time were both groups were actually receiving the same therapy. However, this results in the exclusion of higher-risk patients who had events within the first 6 months. Moreover, the fact that patients had to present to hospital at 6 months after intervention in order to be assessed for eligibility may have introduced additional selection bias favouring inclusion of lower-risk patients. Second, there may have been an inherent reluctance of treating physicians to enrol patients in a study that includes the possibility of allocation to a shorter duration of DAPT. This is reflected in the slower than expected recruitment and the early termination of enrolment. This also likely resulted in the inclusion of patients perceived to be at lower risk of adverse events. Third, while the assumptions for the event rates were based on data from patients treated with early generation DES, the trial mainly enrolled patients treated with newer generation DES, with only 11% of patients having received treatment with early generation DES. Newer generation stents have been shown to be associated with lower rates of adverse clinical events in general, and stent thrombosis in particular, when compared with early generation devices.[22,23]

Although there was no significant difference in the primary endpoint between centres that were monitored (1.6%) and those without monitoring (1.2%, $P = 0.36$; also see *Figure 6*), it is difficult to distinguish between the impact of monitoring and centre variability in the slight numerical difference in outcomes.

We performed a *post hoc* sample size calculation with the actually observed incidence of the combined primary endpoint of 1.6% in the 12-month group and applied the same relative margin of non-inferiority of 20% for assessing non-inferiority of the 6-month group. With a power of 80% and a one-sided α-level of 0.05 the required sample size increased to >40 000 patients.

The main finding of the ISAR-SAFE trial was that we did not find a significant difference in net clinical outcome with 6 months of clopidogrel compared with 12 months of therapy. The results are in line with the recently published ITALIC study.[21] Regarding the choice of the primary endpoint, two features deserve further mention. First, the use of net clinical endpoints to capture both ischaemic and bleeding events in a single composite endpoint is sometimes questioned. Indeed, it must be acknowledged that drawing definitive conclusions from studies of treatments that have opposite effects on ischaemic and bleeding complications is inherently challenging. However, net clinical outcome better reflects mortality and morbidity, the prevention of which remains the main goal of clinical trials on cardiovascular treatment. Moreover, as both bleeding and ischaemic events have been shown to be strong and independent predictors of long-term mortality after PCI,[24] we believe that the use of net clinical outcome is appropriate in this setting. Second, the time point of assessment

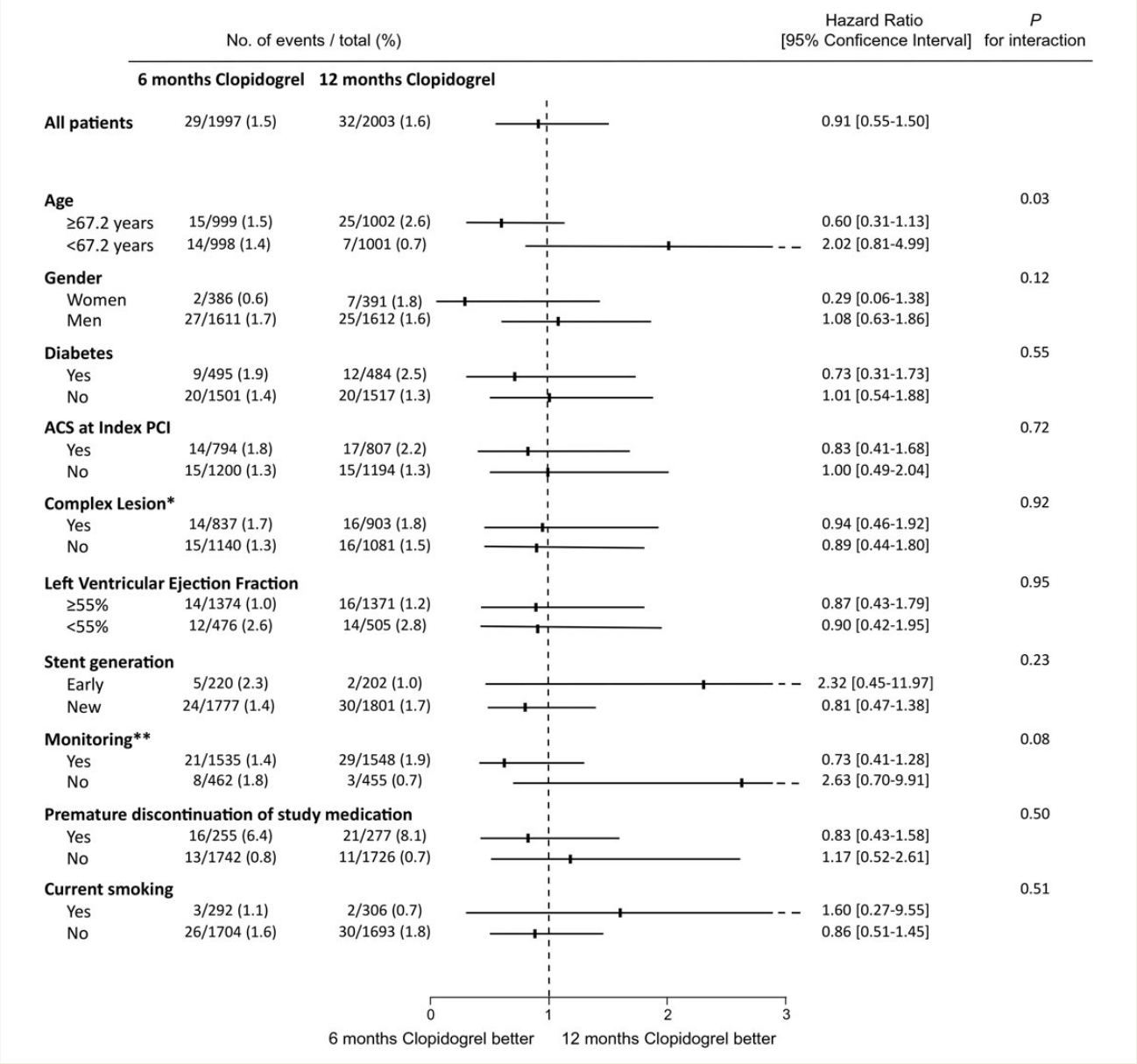

Figure 6 Incidence of the primary endpoint in subgroups. *Complex lesions were defined as type B2 or C lesions according to the modified American College of Cardiology/American Heart Association classification. **Study monitoring of centres.

for the primary endpoint was defined at 9 months after enrolment (or 3 months after the completion of the study treatment). The rationale for this choice was based on concerns regarding a potential for a clustering of ischaemic events after discontinuation of clopidogrel due to a so-called rebound phenomenon.[19] Subsequent platelet function and clinical studies failed to support these concerns.[25,26] In fact in our study we found that results at 6 months after enrolment were concordant with those at the time point of the primary analysis.

Examination of the individual components of the primary endpoint revealed similar rates of both ischaemic and bleeding events in the two treatment groups. In terms of ischaemic events the composite of death, myocardial infarction, stent thrombosis, and stroke was low and similar in both groups. Although the results of our trial must be interpreted cautiously in light of the above-mentioned limitations, these data are consistent with earlier studies comparing shorter duration vs. longer duration of DAPT after DES implantation[8–13,15] and in line with a number of recent meta-analyses of clinical trials.[14,27]

In terms of bleeding events, we also failed to detect a significant difference in major bleeding between the two treatment groups. Nevertheless, more sensitive and recent measures of bleeding assessment such as BARC showed an increased risk with 12-month clopidogrel, which might also have prognostic impact.[28] The finding in relation to major bleeding is somewhat at odds with prior data[14,27] though the dilution of expected differences in bleeding events between the two groups might also be related to the time

point of randomization at 6 months after treatment, and the consequent exclusion of higher bleeding risk patients.

The results of the trial were consistent across pre-specified subgroups of gender, diabetes mellitus, ACS, complex lesion morphology, and left ventricular function. However, there was a significant interaction between age and treatment effect regarding net clinical outcome, suggesting a benefit with shorter duration of clopidogrel therapy in older and longer duration in younger patients. While this finding might be considered as hypothesis-generating interpretation of differences in subgroups is challenging especially in trials with no evidence of treatment effect in the overall population. In relation to stent type implanted at baseline, although there is good evidence that newer generation DES are superior to earlier generation DES in terms of efficacy and safety[23] we were not able to find an interaction between DES generation and treatment effect in the *post hoc* subgroup analysis. This may be related to the low number of earlier generation DES in this study as well as to the overall low event rates.

A notable feature of our trial is that 40% of patients enrolled had a diagnosis of ACS at the time of the index intervention. Indeed the enrolment of these patients is in line with prior randomized trials that tested a reduced duration of clopidogrel therapy after DES,[9–11] although current guidelines in both Europe and the USA recommend a 12-month therapy irrespective of type of stent received.[6,7] However, no interaction for treatment effect was seen for patients with ACS. Yet, these data cannot serve as a source of evidence to support reduction of the duration of DAPT in these patients.

Our study has some important additional limitations. First, clopidogrel was the only ADP-receptor antagonist investigated in our study. Accordingly, results may not be generalized to patients treated with newer, more potent ADP-receptor antagonists. Second, our trial was not designed to assess the risks and benefits of DAPT duration beyond 12 months. A previous open-label, randomized trial did not find a benefit of an extension of DAPT compared with aspirin alone in patients who were on DAPT and event free at 12 months after DES implantation in terms of cardiac death or myocardial infarction.[8] However, the large-scale, randomized, double-blind, placebo-controlled DAPT study which evaluated the extension of DAPT from 12 to 30 months showed a significant reduction in stent thrombosis and major adverse cardiac and cerebrovascular events but an increased risk of bleeding with prolonged therapy. Yet, the interpretation of the results was made difficult by the finding of a higher all-cause mortality in the latter group.[29]

Moreover, several DES have received CE mark approval for DAPT durations of 1 or 3 months. The value of this shorter DAPT duration was not addressed in the ISAR-SAFE trial. Finally, we used a one-sided α-level of 0.05 and we acknowledge that the use of an α-level of 0.025 would have been more conservative.

In conclusion, in this international, multicentre, randomized, double-blind, placebo-controlled trial, characterized by low event rates, we did not observe a significant difference between 6 and 12 months of clopidogrel after DES implantation regarding net clinical outcome, the composite of death, myocardial infarction, stent thrombosis, stroke, and major bleeding. However, the results of the trial must be considered in view of its premature termination and lower than expected event rates.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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