



Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation

The ISAR-TRIPLE Trial

Katrin A. Fiedler, MD,* Michael Maeng, MD,† Julinda Mehilli, MD,‡§ Stefanie Schulz-Schüpke, MD,* Robert A. Byrne, MB, BCh, PhD,*§ Dirk Sibbing, MD,‡§ Petra Hoppmann, MD,|| Simon Schneider, MD,|| Massimiliano Fusaro, MD,* Ilka Ott, MD,* Steen D. Kristensen, MD,† Tareq Ibrahim, MD,|| Steffen Massberg, MD,‡§ Heribert Schunkert, MD,*§ Karl-Ludwig Laugwitz, MD,§|| Adnan Kastrati, MD,*§ Nikolaus Sarafoff, MD,‡

ABSTRACT

BACKGROUND Patients receiving oral anticoagulation (OAC) who undergo drug-eluting stent (DES) implantation require additional dual antiplatelet therapy with aspirin and clopidogrel. Such triple therapy confers an elevated bleeding risk, and its optimal duration is not known.

OBJECTIVES The goal of this study was to evaluate whether shortening the duration of clopidogrel therapy from 6 months to 6 weeks after DES implantation was associated with a superior net clinical outcome in patients receiving concomitant aspirin and OAC.

METHODS In this randomized, open-label trial, we enrolled patients receiving OAC who underwent DES implantation at 3 European centers between September 2008 and December 2013. A total of 614 patients receiving concomitant aspirin and OAC were randomized to either 6-week clopidogrel therapy (n = 307) or 6-month clopidogrel therapy (n = 307). The primary endpoint was a composite of death, myocardial infarction (MI), definite stent thrombosis, stroke, or Thrombolysis In Myocardial Infarction (TIMI) major bleeding at 9 months.

RESULTS The primary endpoint occurred in 30 patients (9.8%) in the 6-week group compared with 27 patients (8.8%) in the 6-month group (hazard ratio [HR]: 1.14; 95% CI: 0.68 to 1.91; p = 0.63). There were no significant differences for the secondary combined ischemic endpoint of cardiac death, MI, definite stent thrombosis, and ischemic stroke (12 [4.0%] vs. 13 [4.3%]; HR: 0.93; 95% CI: 0.43 to 2.05; p = 0.87) or the secondary bleeding endpoint of TIMI major bleeding (16 [5.3%] vs. 12 [4.0%]; HR: 1.35; 95% CI: 0.64 to 2.84; p = 0.44).

CONCLUSIONS Six weeks of triple therapy was not superior to 6 months with respect to net clinical outcomes. These results suggest that physicians should weigh the trade-off between ischemic and bleeding risk when choosing the shorter or longer duration of triple therapy. (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation [ISAR-TRIPLE]; [NCT00776633](https://clinicaltrials.gov/ct2/show/study/NCT00776633)) (J Am Coll Cardiol 2015;65:1619-29) © 2015 by the American College of Cardiology Foundation.

From the *Deutsches Herzzentrum München, Technische Universität, Klinik für Herz- und Kreislauferkrankungen, Munich, Germany; †Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; ‡Klinikum der Universität München, Ludwig-Maximilians-Universität, Medizinische Klinik und Poliklinik I, Munich, Germany; §Deutsches Zentrum für Herz Kreislauferforschung, partner site Munich Heart Alliance, Munich, Germany; and the ||Klinikum rechts der Isar, Technische Universität, I. Medizinische Klinik und Poliklinik, Munich, Germany. The study sponsor was Deutsches Herzzentrum München. The study was supported in part by an unrestricted research grant from Abbott, Deutsches Herzzentrum München, and PCI Research at Aarhus University Hospital. Neither the sponsor nor the research grant providers had any role in study design, data collection, data analysis, data interpretation, or writing of the report, and they did not review or comment on this report. Dr. Mehilli has received fees for lectures and advisory boards from Abbot Vascular, Terumo, and Lilly/Daiichi-Sankyo. Dr. Sibbing has received speaker fees and honoraria for consulting from Eli Lilly, Daiichi-Sankyo, Bayer Vital, AstraZeneca, Verum Diagnostica, and Roche



ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

BMS = bare-metal stent(s)

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

MI = myocardial infarction

OAC = oral anticoagulation

PCI = percutaneous coronary intervention

ST = stent thrombosis

TIMI = Thrombolysis In Myocardial Infarction

Patients undergoing percutaneous coronary intervention (PCI) require dual antiplatelet therapy (DAPT) consisting of aspirin and a thienopyridine, a regimen proven superior to oral anticoagulation (OAC) for the prevention of subsequent stent thrombosis (1,2). However, randomized trials have shown that DAPT is inferior to OAC for reducing the risk of thromboembolic events in patients with atrial fibrillation (3) or with mechanical heart valves (4). Accordingly, it is recommended that patients receiving OAC and undergoing PCI receive triple therapy, typically consisting of aspirin, clopidogrel, and an oral anticoagulant (5,6).

SEE PAGE 1630

The optimal duration of triple therapy after PCI remains to be defined, and 2 factors need consideration. First, the risk of stent thrombosis (ST) is highest in the early phase after PCI and declines over time (7). Secondly, the risk of bleeding with triple therapy increases with duration of therapy (8,9) and intensity of OAC (10). Current guidelines for patients on OAC undergoing PCI were drafted mainly on the basis of observational data and state that a minimum of 4 weeks of triple therapy after bare-metal stent (BMS) implantation and 1 to 12 months of therapy after drug-eluting stent (DES) implantation should be considered (5,6,11,12). On the basis of data from 1 randomized trial (13), dual therapy of an OAC and clopidogrel may be considered as an alternative to initial triple therapy in selected patients (6,11). The duration of therapy after DES implantation is a matter of particular importance because patients are sometimes denied this highly effective treatment due to a perceived need for extended-duration triple therapy.

The objective of the ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen-Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting

Stenting) trial was to assess whether a 6-week clopidogrel treatment after DES implantation was associated with a superior net clinical outcome compared with a 6-month clopidogrel treatment in patients receiving concomitant aspirin and OAC.

METHODS

STUDY DESIGN AND PATIENTS. In this randomized, open-label trial, we enrolled patients at 2 centers in Germany (Deutsches Herzzentrum and Klinikum rechts der Isar, both in Munich) and at 1 center in Denmark (Aarhus University Hospital in Aarhus) between September 2008 and December 2013. Eligible patients must have been receiving OAC for at least 12 months and receiving a DES for stable angina or acute coronary syndrome. Major exclusion criteria were age ≤ 18 years, previous ST, DES implantation in the left main stem, active bleeding or bleeding diathesis, or a history of intracranial bleeding. The design and rationale of the ISAR-TRIPLE trial, including the full list of exclusion criteria, was reported previously (14).

The study was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The institutional ethics committee responsible for the participating centers approved the trial protocol. All patients provided written informed consent.

RANDOMIZATION. Randomization to a 6-week versus 6-month duration of clopidogrel therapy after DES implantation was performed with a treatment allocation of 1:1 by means of sealed opaque envelopes containing a computer-generated sequence (ISAR-research Centre, Munich) for the German patients and by a computer-generated web-based system (Aarhus University Hospital, Aarhus) for the Danish patients. Patients were considered enrolled in the study and eligible for the final intention-to-treat analysis at the time of randomization.

TREATMENT. Coronary angiography was performed according to conventional and local standards. No

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recommendation was provided in the protocol regarding the vascular access site. Patients received a loading dose of clopidogrel 300 to 600 mg before PCI. Peri-interventional therapy with heparin or bivalirudin was at the discretion of the treating physician, and glycoprotein IIb/IIIa inhibitor use was discouraged. Aspirin-naïve patients received 500 mg of intravenous aspirin. Because the study was unblinded, commercially available drugs were given according to the protocol. During the study, patients received clopidogrel 75 mg daily for 6 weeks or 6 months; aspirin 75 to 200 mg once daily, according to local standards; and a vitamin K antagonist with either phenprocoumon or warfarin. OAC therapy was prescribed with the lowest recommended target international normalized ratio (INR) during the duration of triple therapy.

ASSESSMENTS AND FOLLOW-UP. Patients were evaluated by telephone call or at physician office visits after 6 weeks, 6 months, and 9 months to obtain detailed information regarding the occurrence of endpoints, adverse events, and patient compliance with the study medication.

The primary endpoint of the study was a composite of death, myocardial infarction (MI), definite ST (15), stroke, or Thrombolysis In Myocardial Infarction (TIMI) major bleeding (16) at 9 months after randomization. Secondary endpoints were the incidence of ischemic complications (cumulative incidence of cardiac death, MI, definite ST, or ischemic stroke) or bleeding complications (TIMI major bleeding), and each individual component of the primary and secondary endpoint was assessed separately. Bleeding events were also classified according to the Bleeding Academic Research Consortium (BARC) criteria (16). A detailed description of the endpoint definitions was recently published (14). Events were adjudicated and classified by an event adjudication committee whose members were unaware of the assigned treatment.

STATISTICAL ANALYSIS. The study was designed to assess whether a 6-week clopidogrel treatment after DES in patients receiving aspirin and OAC was associated with a net clinical outcome (composite of death, MI, definite ST, stroke, or TIMI major bleeding) superior to that of a 6-month clopidogrel treatment in patients receiving aspirin and OAC. The incidence of the primary endpoint was assumed to be 10% with a 6-month clopidogrel therapy and a risk reduction of 60% with a 6-week clopidogrel therapy; a power of 80% and an alpha level of 0.05 were applied. Accordingly, 283 patients were needed in each group.

Categorical variables, such as demographics and medical history data, were summarized using frequencies and proportions and were compared using the chi-square test or Fisher exact test, as appropriate. Continuous data were summarized using mean $\pm$ SD or median (25th, 75th percentiles) and compared using the Student *t* test or nonparametric Wilcoxon rank-sum test. All tests were 2 sided, and an alpha level of 0.05 was considered statistically significant. No adjustments were made for the primary and secondary endpoint comparisons. Risk estimates were calculated by Cox analysis. The Kaplan-Meier method was used for building event curves. For assessment of events occurring after 6 weeks, a post-hoc landmark analysis was performed. Analysis of the primary endpoint was performed in pre-specified subgroups defined by age, sex, diabetes, history of stroke, history of bleeding, hypertension, clinical presentation, indication for OAC, ejection fraction, and renal function. The interaction between the assigned treatment and baseline variable with respect to the primary endpoint was assessed by the interaction term being entered into the respective Cox proportional model to check the heterogeneity of treatment differences across the levels of a baseline variable. We did sample size calculation with nQuery Advisor (version 7.0, Statistical Solutions, Cork, Ireland). All statistical analyses were performed with the software R (version 2.15.0).

RESULTS

PATIENTS. A total of 614 patients were enrolled, of whom 307 were randomly assigned to the 6-week group and 307 to the 6-month group (Online Figure 1). Table 1 shows baseline clinical and demographic characteristics of the patients. Atrial fibrillation or flutter was the indication for OAC in 254 patients (82.7%) in the 6-week group and 261 patients (85.0%) in the 6-month group. Approximately two-thirds of all patients presented with stable angina. Ninety-eight percent of patients underwent catheterization using femoral access. The majority of patients received new-generation DES (Table 2). All but 1 patient received unfractionated heparin during the procedure, and no patient received glycoprotein IIb/IIIa inhibitors.

Aspirin therapy was used in 96.7%, 95.0%, and 96.0% of patients at the 6-week, 6-month, and 9-month follow-up time points, respectively, with no difference between the 2 groups. OAC therapy was used in 93.7%, 90.6%, and 88.5% of patients at 6 weeks, 6 months, and 9 months, respectively, with no difference between the 2 groups. Median INR

TABLE 1 Clinical Characteristics and Treatment

	6-Week Group (n = 307)	6-Month Group (n = 307)
Clinical baseline characteristics		
Age, yrs	73.9 ± 7.7	73.3 ± 8.7
Female	78 (25.4)	65 (21.2)
Body mass index, kg/m ²	27.5 ± 4.2	27.9 ± 4.6
Diabetes	85 (27.7)	72 (23.5)
Insulin dependent	24 (7.8)	23 (7.5)
Arterial hypertension	236 (76.9)	232 (75.6)
Hypercholesterolemia	227 (73.9)	230 (74.9)
Current smoker	28 (9.1)	32 (10.4)
History of myocardial infarction	90 (29.3)	76 (24.8)
History of CABG*	73 (23.8)	51 (16.6)
Multivessel disease	221 (72.0)	216 (70.3)
Clinical presentation on admission		
STEMI	3 (1.0)	2 (0.7)
NSTEMI	50 (16.3)	41 (13.4)
Unstable angina pectoris	49 (16.0)	52 (16.9)
Stable angina pectoris	205 (66.8)	212 (69.1)
Medication at discharge		
Aspirin	307 (100)	307 (100)
Clopidogrel	307 (100)	307 (100)
Beta-blocker	265 (86.3)	269 (87.6)
ACE inhibitor	197 (64.2)	198 (64.5)
ARB	71 (23.1)	72 (23.4)
Calcium-channel blocker	70 (22.8)	79 (25.7)
Diuretic	210 (68.4)	202 (65.8)
Statin	262 (85.3)	260 (84.7)
Indication for oral anticoagulation†		
Atrial fibrillation or flutter	254 (82.7)	261 (85.0)
Mechanical valve	17 (5.5)	28 (9.1)
Venous thromboembolism	23 (7.5)	11 (3.6)
Other	13 (4.2)	7 (2.3)
Stroke risk for patients with AF‡		
CHADS ₂ score		
0	5 (2.0)	5 (1.9)
1	37 (14.6)	50 (19.2)
2	79 (31.1)	90 (34.5)
3	76 (29.9)	78 (29.9)
4	36 (14.2)	28 (10.7)
5	15 (5.9)	7 (2.7)
>5	6 (2.3)	3 (1.1)
CHA ₂ DS ₂ -VASc Score		
1	0	1 (0.4)
2	12 (4.7)	18 (6.9)
3	27 (10.6)	42 (16.1)
4	69 (27.2)	70 (26.8)
5	70 (27.6)	74 (28.4)
6	50 (19.7)	38 (14.6)
7	16 (6.3)	14 (5.4)
8	8 (3.1)	2 (0.8)
9	2 (0.8)	2 (0.8)

Values are mean ± SD or n (%). *p = 0.03. †p = 0.03. ‡n = 254 in the 6-week group and n = 261 in the 6-month group.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; CHADS₂ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack; CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Angiographic Characteristics According to Treated Lesions

	6-Week Group (n = 417)	6-Month Group (n = 409)
Stent type		
EES	158 (37.9)	160 (39.1)
Biodegradable polymer BES	69 (16.5)	64 (15.7)
Biodegradable polymer SES	62 (14.9)	70 (17.1)
ZES	45 (10.8)	46 (11.2)
Probucol SES	45 (10.8)	46 (11.2)
PES	20 (4.8)	12 (2.9)
SES	9 (2.1)	4 (1.0)
Bioresorbable EES	4 (1.0)	3 (0.7)
BMS*	2 (0.5)	0
DEB/PTCA†	3 (0.7)	4 (1.0)
PCI vessel		
LAD	177 (42.4)	173 (42.3)
LCX	102 (24.5)	73 (17.8)
RCA	110 (26.4)	143 (35.0)
Left main stem‡	7 (1.7)	5 (1.2)
Bypass graft	21 (5.0)	15 (3.7)
Stented length, mm	25.3 ± 13.3	25.6 ± 13.3
Stents per lesion	1.3 ± 0.5	1.3 ± 0.5

Values are n (%) or mean ± SD. *One patient had 1 EES 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. ‡Four of the 7 left main stem lesions in the 6-week group and 4 of the 5 main stem lesions in the 6-month group had a previous bypass graft.

BES = biolimus-eluting stent; BMS = bare-metal stent(s); EES = everolimus-eluting stent(s); LAD = left anterior descending; LCX = left circumflex; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); PTCA/DEB = percutaneous transluminal coronary angioplasty/drug-eluting balloon; RCA = right coronary artery; SES = sirolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

values (interquartile range) were 2.2 (1.9 to 2.7), 2.3 (2.0 to 2.6), and 2.3 (2.0 to 2.6) at 6 weeks, 6 months, and 9 months, respectively, with no difference between the 2 groups. At 6 weeks, 6 months, and 9 months, INR values were within the therapeutic range (2.0 to 3.0) in 63.7%, 68.9%, and 66.1% of patients, respectively, with no difference between the 2 groups.

At discharge, 37.3% of patients were treated with proton pump inhibitors, with no difference between groups.

OUTCOMES. Follow-up at 9 months was completed for 302 patients (98.4%) assigned to 6-week therapy and 304 patients (99.0%) assigned to 6-month therapy. The primary endpoint of death, MI, definite ST, stroke, or TIMI major bleeding occurred in 30 patients (9.8%) in the 6-week group compared with 27 patients (8.8%) in the 6-month group (hazard ratio [HR]: 1.14; 95% CI: 0.68 to 1.91; p = 0.63) at 9 months (Figure 1A, Table 3). The lack of treatment effect was consistent across all pre-specified subgroups defined by age, sex, diabetes, history of stroke, history of bleeding,

hypertension, clinical presentation, indication for OAC, ejection fraction, and renal function (Online Figure 2).

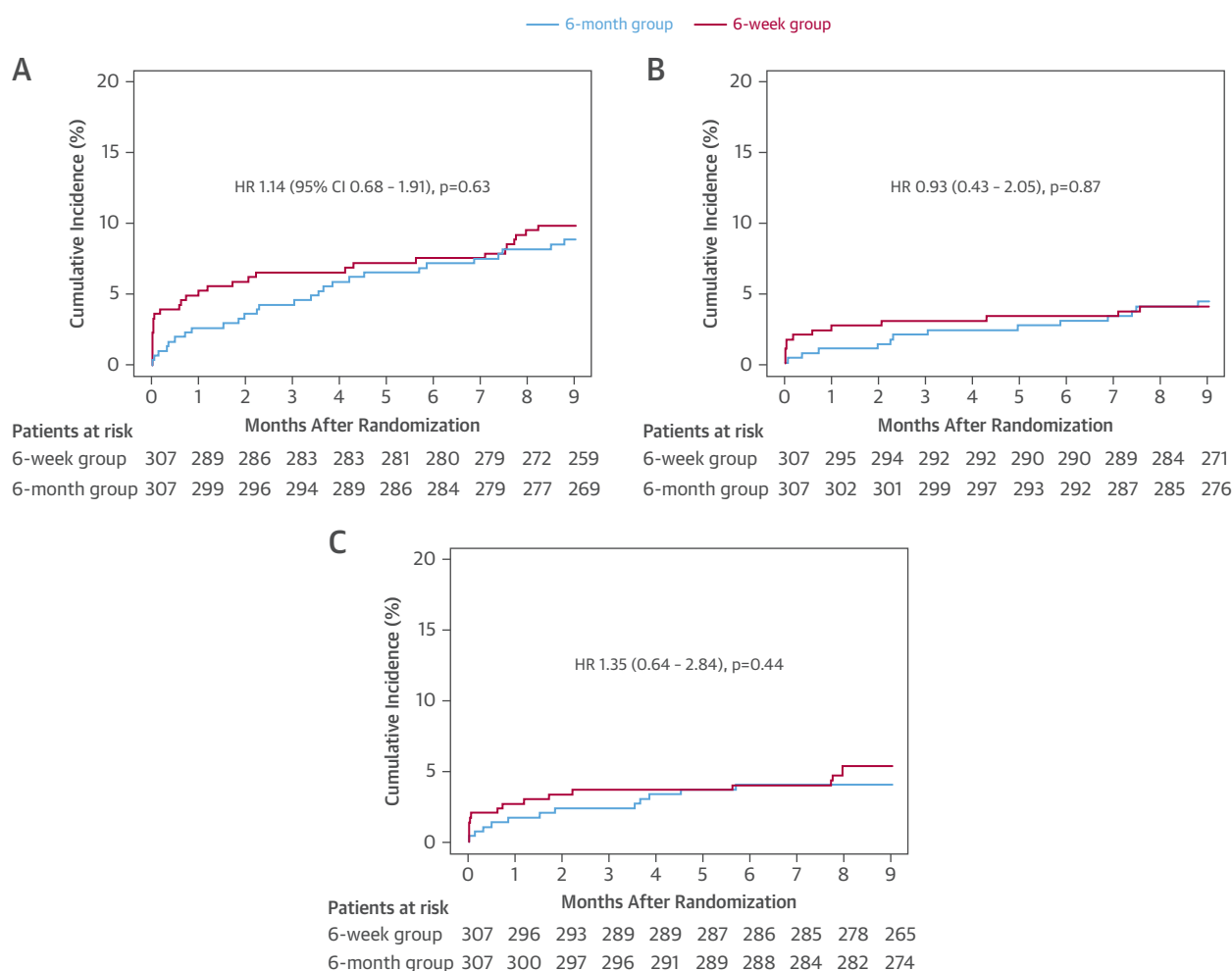
Regarding secondary endpoints, the combined ischemic endpoint of cardiac death, MI, definite ST, or ischemic stroke was reported in 12 patients (4.0%) in the 6-week group and 13 patients (4.3%) in the 6-month group (HR: 0.93; 95% CI: 0.43 to 2.05; $p = 0.87$) (Figure 1B). There were 6 cases (2.0%) of MI in the 6-week group, compared with none in the 6-month group ($p = 0.03$). Three MIs were periprocedural, occurring within 24 h of PCI; 1 patient had definite ST on the day of PCI; 1 patient had definite ST on day 17 while receiving triple therapy; and

1 MI occurred on day 212 while the patient was receiving OAC and aspirin.

A potential rebound phenomenon was the reason for moving the endpoints from 6 to 9 months. Without this 3-month extension, a possible rebound phenomenon would have disadvantaged only the 6-week group. However, Figure 1B shows no excess ischemic events in either group in the 3 months following the discontinuation of study treatment.

There was no difference in TIMI major bleeding between the 2 groups (16 [5.3%] vs. 12 [4.0%]; HR: 1.35; 95% CI: 0.64 to 2.84; $p = 0.44$) (Figure 1C). Any BARC bleeding occurred in 114 patients (37.6%) in the 6-week group and 122 patients (40.2%) in the

FIGURE 1 Cumulative Incidence of the Primary, Secondary Ischemic, and Secondary Bleeding Endpoints



Kaplan-Meier analysis of the (A) primary endpoint (cumulative incidence of death, myocardial infarction, stent thrombosis, stroke or Thrombolysis In Myocardial Infarction [TIMI] major bleeding), (B) secondary ischemic endpoint (cardiac death, myocardial infarction, stent thrombosis, or ischemic stroke), and (C) secondary bleeding endpoint (TIMI major bleeding) at 9 months. HR = hazard ratio.

TABLE 3 Results for Primary and Secondary Endpoints at 9 Months and in Landmark Analysis From 6 Weeks to 9 Months

	Outcome at 9 Months				Landmark Analysis 6 Weeks to 9 Months			
	6-Week Group (n = 307)	6-Month Group (n = 307)	Hazard Ratio (95% CI)	p Value	6-Week Group	6-Month Group	Hazard Ratio (95% CI)	p Value
Primary endpoint								
Death, MI, stent thrombosis, stroke or major bleeding	30 (9.8)	27 (8.8)	1.14 (0.68-1.91)	0.63	13 (4.6)	19 (6.4)	0.70 (0.35-1.42)	0.32
Secondary endpoints								
Cardiac death, myocardial infarction stent thrombosis or ischemic stroke	12 (4.0)	13 (4.3)	0.93 (0.43-2.05)	0.87	4 (1.4)	10 (3.4)	0.40 (0.13-1.24)	0.13
TIMI major bleeding	16 (5.3)	12 (4.0)	1.35 (0.64-2.84)	0.44	7 (2.4)	7 (2.4)	1.01 (0.35-2.88)	0.99
Death	12 (4.0)	16 (5.2)	0.75 (0.35-1.59)	0.45	8 (2.7)	12 (4.0)	0.66 (0.27-1.63)	0.37
Cardiac death	5 (1.7)	9 (3.0)	0.56 (0.19-1.66)	0.29	3 (1.0)	8 (2.7)	0.37 (0.10-1.34)	0.15
MI	6 (2.0)	0	—	0.03	1 (0.03)	0	—	>0.99
Periprocedural MI	3 (1.0)	0	—	0.25	—	—	—	—
Definite stent thrombosis	2 (0.7)	0	—	0.50	0	0	—	—
Stroke	4 (1.3)	6 (2.0)	0.67 (0.19-2.35)	0.53	2 (0.7)	2 (0.7)	0.99 (0.14-7.05)	0.99
Ischemic stroke	3 (1.0)	4 (1.3)	0.75 (0.17-3.34)	0.71	1 (0.03)	2 (0.7)	0.5 (0.05-5.24)	0.57
TIMI major and minor bleeding	35 (11.5)	30 (9.9)	1.18 (0.73-1.93)	0.49	14 (5.0)	15 (5.2)	0.95 (0.46-1.97)	0.90
TIMI major bleeding	16 (5.3)	12 (4.0)	1.35 (0.64-2.84)	0.44	7 (2.4)	7 (2.4)	1.01 (0.35-2.88)	0.99
TIMI minor bleeding	19 (6.3)	18 (5.9)	1.06 (0.56-2.03)	0.85	7 (2.4)	8 (2.8)	0.88 (0.32-2.44)	0.81
Any BARC bleeding	114 (37.6)	122 (40.2)	0.94 (0.73-1.21)	0.63	48 (20.5)	70 (27.9)	0.68 (0.47-0.98)	0.04
BARC 1	58 (19.4)	57 (19.1)	1.03 (0.72-1.49)	0.87	28 (10.6)	37 (13.4)	0.76 (0.47-1.25)	0.29
BARC 2	22 (7.3)	33 (10.9)	0.66 (0.38-1.13)	0.13	7 (2.5)	17 (6.0)	0.40 (0.17-0.97)	0.04
BARC 3a	14 (4.6)	17 (5.6)	0.83 (0.41-1.68)	0.60	4 (1.4)	8 (2.8)	0.50 (0.15-1.63)	0.26
BARC 3b	17 (5.6)	13 (4.3)	1.32 (0.64-2.72)	0.45	7 (2.4)	8 (2.7)	0.89 (0.32-2.44)	0.81
BARC 3c	0	0	—	—	0	0	—	—
BARC 4	0	0	—	—	0	0	—	—
BARC 5a	0	1 (0.03)	—	>0.99	0	0	—	—
BARC 5b	3 (1.0)	1 (0.03)	3.00 (0.34-25.8)	0.34	2 (0.7)	0	—	0.50
BARC bleeding $\geq$ 2	56 (18.4)	65 (21.3)	0.86 (0.60-1.23)	0.41	20 (7.6)	33 (12.2)	0.60 (0.34-1.04)	0.07

Values are n (Kaplan Meier Estimates), unless otherwise noted.
BARC = Bleeding Academic Research Consortium criteria; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction criteria.

6-month group (HR: 0.94; 95% CI: 0.73 to 1.21; $p = 0.63$) (Figure 2A). Intracranial bleeding frequency was low (Online Table 1). More than one-half of all bleedings were localized in the nose or skin, followed by gastrointestinal and access site bleeds.

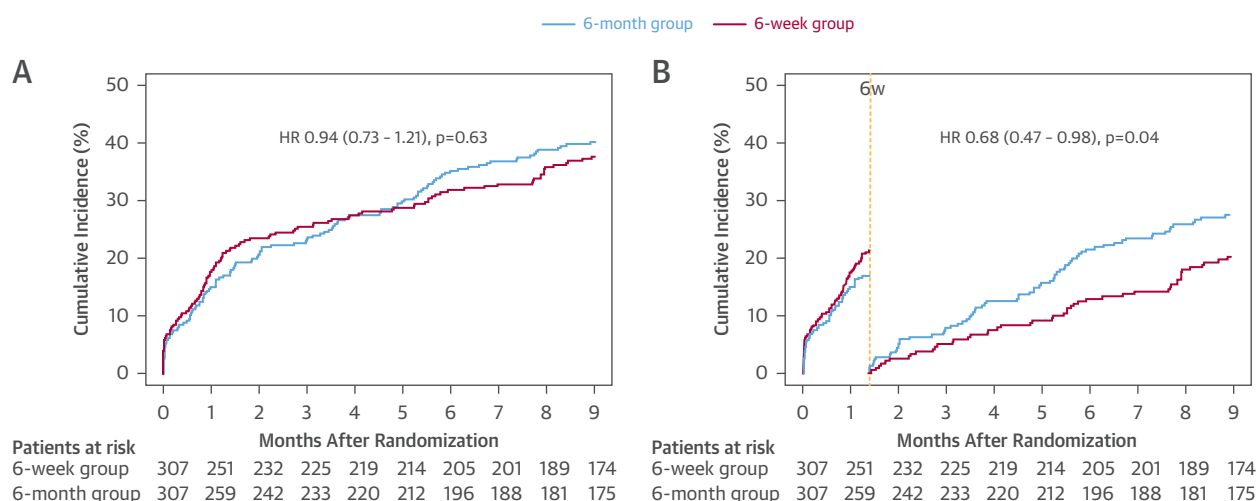
Compliance with assigned clopidogrel therapy at 6 weeks was 97.7% in the 6-week group and 98.4% in the 6-month group ($p = 0.56$), 73.6% and 86.6% ($p < 0.001$) at 6 months, and 76.6% and 64.5% ($p < 0.001$) at 9 months (Online Figure 1). Of patients who were nonadherent to clopidogrel therapy at 6 months, the primary endpoint occurred in 13 of 81 (16.0%) in the 6-week group and 3 of 41 (7.7%) in the 6-month group. The secondary ischemic endpoint occurred in 6 patients (7.4%) in the 6-week group and none in the 6-month group. The secondary TIMI major bleeding endpoint occurred in 5 patients (6.3%) in the 6-week group and 2 patients (4.9%) in the 6-month group.

LANDMARK ANALYSES. By protocol, both groups were treated with the same triple therapy regimen

for the first 6 weeks. Thereafter, 1 group received aspirin and OAC only, whereas the other group continued the triple therapy regimen until 6 months. To compare outcomes attributed to the period when treatment between the groups separated, we performed a post-hoc landmark analysis from 6 weeks to 9 months, which revealed no significant differences regarding the primary or secondary endpoints (Table 3). There were significantly fewer bleeding events according to any BARC bleeding (48 [20.5%] vs. 70 [27.9%]; HR: 0.68; 95% CI: 0.47 to 0.98; $p = 0.04$) in landmark analysis of the 6-week group (Figure 2B, Table 3) and fewer bleeding events according to the cumulative incidence of BARC type 2 or higher bleeding in landmark analysis of the 6-week group (Central Illustration).

We also performed a landmark analysis for the time period when recommendations for treatment were truly different. In the landmark analysis from 6 weeks to 6 months, there were no significant differences regarding the primary or secondary endpoints. This

FIGURE 2 Cumulative Incidence of BARC Types 1 to 5 Bleeding at 9 Months and in Landmark Analysis



Kaplan-Meier analysis of Bleeding Academic Research Consortium (BARC) types 1 to 5 bleeding at 9 months (**A**) and in landmark analysis before and after 6 weeks (**B**). Other abbreviation as in [Figure 1](#).

analysis revealed an even more pronounced reduction in bleeding complications in the 6-week group according to any BARC bleeding, BARC type 2 bleeding, and the cumulative incidence of BARC type 2 or higher bleeding ([Online Table 2](#)).

DISCUSSION

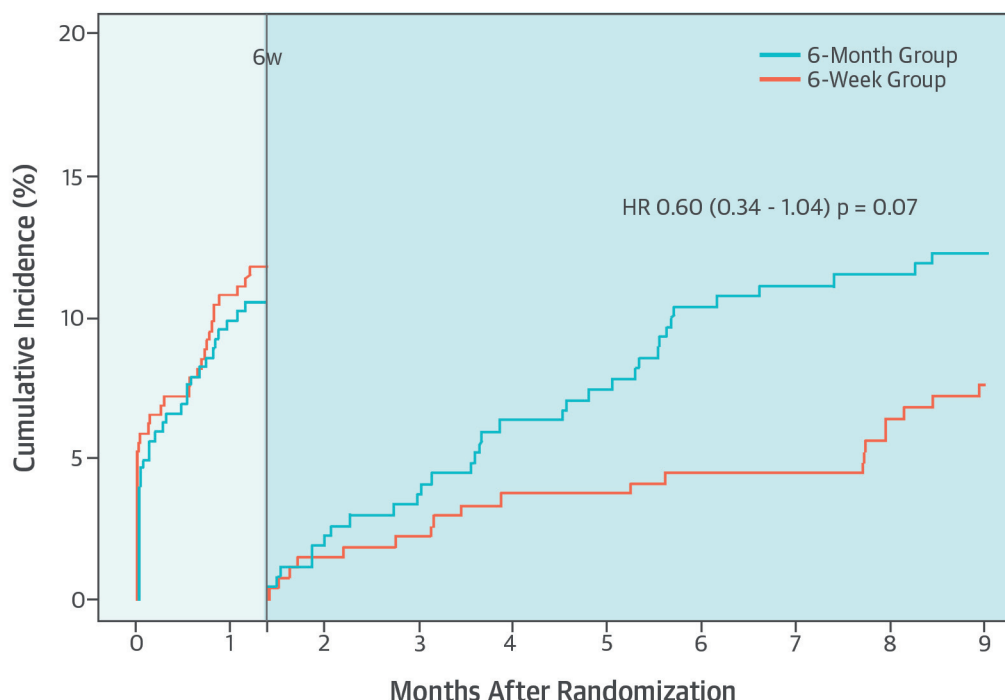
In this randomized trial of patients with an indication for OAC undergoing DES implantation, we compared regimens of 6 weeks and 6 months of clopidogrel therapy in the setting of concomitant aspirin and OAC therapy. The main findings are as follows: 1) 6 weeks compared with 6 months of triple therapy was not superior with regard to net clinical outcomes and 2) neither the composite of ischemic complications nor major bleedings was statistically significantly different between the treatment groups.

Balancing ischemic and bleeding risk is of the utmost importance in patients treated with clopidogrel, especially in those receiving triple therapy. Premature discontinuation of antiplatelet therapy might increase the risk of ST (7), whereas prolonged therapy has been associated with more bleeding events (8). Current recommendations for duration of triple therapy in patients on OAC undergoing coronary stent implantation differ between European and North American consensus statements (5,6). Whereas European authorities recommend triple therapy durations after DES implantation of 1 to

6 months, North American experts mostly recommend a 12-month course (5,17). This discordance is not surprising because the current evidence for DAPT duration in patients on OAC is lacking. DAPT is generally recommended for at least 4 weeks for BMS and 6 months for DES. In the current trial, 6 weeks of DAPT was chosen to provide patients receiving DES with a DAPT duration close to that required in patients receiving BMS, under the assumption that further protection from ST might also be offered by the presence of OAC. Additionally, the optimal duration of clopidogrel therapy after DES implantation in patients not receiving OAC has shown no uniform results (18,19). Indeed, there is recent evidence to support the use of shorter durations of DAPT in selected patients receiving newer-generation DES not concomitantly treated with OAC (20-23).

The ISAR-TRIPLE trial is the first trial evaluating the optimal duration of clopidogrel therapy in patients treated with DES who have an indication for OAC. The principal finding was that the primary endpoint—a composite of death, MI, ST, stroke, or TIMI major bleeding, also referred to as net clinical outcome—was not superior after a 6-week compared with 6-month duration of triple therapy. Because both ischemic and bleeding events impact mortality after PCI (24,25), net clinical outcome was chosen as the primary endpoint to reflect the aggregate effect on patient outcomes. This is in keeping with prior studies of antithrombotic and antiplatelet therapy

CENTRAL ILLUSTRATION Duration of Triple Therapy: Cumulative Incidence of BARC Type ≥ 2 Bleeding Before and After 6 Weeks



Patients at Risk										
6-Week Group	307	272	264	261	257	256	254	253	245	231
6-Week Group	307	275	267	262	255	251	243	238	236	228

Fiedler, K.A. et al. J Am Coll Cardiol. 2015; 65(16):1619-29.

Kaplan-Meier analysis of Bleeding Academic Research Consortium (BARC) type ≥ 2 bleeding before and after 6 weeks (6w). HR = hazard ratio.

in PCI (26). The power in our study was calculated on the basis of our expectation of a considerable decrease in the number of bleeding complications. Although it might be argued that the magnitude of the assumed reduction was high, the difference in the duration of exposure to triple therapy in both groups was large. Moreover, previous trials also assumed—and were able to demonstrate—a reduction in the number of bleeding complications on the order of 60% (13), and observational data have shown that the frequency of bleeding events may be reduced by 40% with dual compared with triple therapy (27). Notwithstanding these concerns, the present trial is the largest randomized trial to date investigating triple therapy after stent implantation.

There was no difference in major bleeding events between patients treated with a 6-week or 6-month duration of clopidogrel therapy. This may at first seem surprising. Indeed, major bleeding (5.3% vs.

4.0%, respectively) defined according to TIMI criteria as well as BARC types 2 to 5 bleeding was similar in both groups. However, the rates of TIMI major bleeding were comparable to those in the earlier WOEST (What Is the Optimal Antiplatelet & Anticoagulant Therapy in Patients With Oral Anti-coagulation and Coronary Stenting) randomized trial, and, in that trial, omitting aspirin also failed to significantly reduce the number of major hemorrhagic complications (13). This underlines the challenge of reducing the risk of major bleeding events in this patient population. The frequency of any bleeding event in this trial was high—approximately 40% of patients suffered from any bleeding according to BARC during the 9-month study period, with no significant difference between the treatment groups. These findings are numerically similar to the results of the WOEST trial, in which the number of any bleeding episodes at 12 months was 44% in patients

receiving triple therapy. Other studies evaluating safety and efficacy of triple therapy have found lower rates of any bleeding events—on the order of 15% to 20% (8,9,28,29); however, populations, bleeding definitions, and study designs differed substantially.

There was also no extra risk of the composite ischemic endpoint with shorter duration therapy observed in the present study. The absence of differences in relation to the composite ischemic endpoint may be important but requires qualification by examination of the individual components of this endpoint. First, the rate of cardiac death was low and comparable in both groups. The overall rate of ST was low in both groups (0.7% vs. 0.0%). This lends some support to the strategy of DAPT for the initial weeks after PCI. The rate of MI was higher in the 6-week group (2.0% vs. 0.0%). This might theoretically represent a signal of reduced efficacy; however, examination of their temporal distribution showed that all of the events occurred at a time point when treatment between groups did not differ (i.e., before 6 weeks or after 6 months). Therefore, this finding cannot be attributed to the shorter duration of clopidogrel therapy and, in our opinion, likely was due to chance. Finally, the rate of stroke was comparable in both groups and was in line with expected risks.

To further evaluate the impact of triple therapy versus the combination of aspirin and OAC alone, we performed a post-hoc landmark analysis for the period after 6 weeks, when treatment regimens between groups differed. No differences were observed for major bleeding events at landmark analysis. However, the 6-month group experienced significantly more bleeding events according to any BARC and BARC types 2 to 5 bleeding. This is of interest because not only major bleeding events, but also BARC types 2 to 5 bleeding, are known to have an impact on patient 1-year survival rates (25). Nevertheless, it must be acknowledged that overall the ISAR-TRIPLE trial failed to show that a shorter duration of clopidogrel, from 6 months to 6 weeks, was associated with lower bleeding rates. An explanation for this finding may be that approximately one-half of all bleeding events occurred in the first 6 weeks after PCI, when both groups received the same therapy consisting of aspirin, clopidogrel, and OAC.

Finally, although our trial was not designed to show noninferiority with 6-week therapy, compared with 6-month therapy, comparable results were seen in both treatment groups. Although these observations require confirmation in future trials, this provides some evidence that DES implantation in these patients may be undertaken without requiring

an extended duration of triple therapy. Nevertheless, this issue is clinically important because it suggests that patients receiving OAC—who are typically older and have more complex coronary artery disease—could be offered standard of care stent implantation with DES and a duration of DAPT comparable to that administered following treatment with BMS.

STUDY LIMITATIONS. First, the ISAR-TRIPLE trial shares the limitation common to all randomized trials with an open-label design. Although we tried to minimize this bias by endpoint analysis according to the intention-to-treat principle, the use of precise criteria for endpoint assessment, and the use of blinded adjudication of events on the basis of original source data, we cannot fully exclude bias. The trial was not specifically powered to detect differences in the individual components of the primary endpoint, and any comparisons should be interpreted with caution. We also acknowledge that the study was only powered to a fairly large reduction (60%) in events, and the interaction tests in the subgroup analyses were also underpowered.

The results of the post-hoc landmark analysis at 6 weeks should be interpreted with caution. Moreover, randomization after 6 weeks might have been more suitable. However, for pragmatic reasons related to feasibility of patient enrollment, a number of recent studies evaluating optimal duration of DAPT after DES implantation have also randomized patients at the time of the index procedure (30,31). We did not investigate the role of new oral anticoagulants or newer, more potent antiplatelet agents because they were not approved at the time the study was designed. Limited data suggest that in the setting of triple therapy, dabigatran, compared with warfarin, may reduce (32) and prasugrel, compared with clopidogrel, may increase (33) bleeding rates. However, the results of this trial will be useful in guiding the duration of therapy in future trials with novel OACs and/or ADP receptor antagonists. Noncompliance with the prescribed clopidogrel regimen was approximately 25% at the 6-month follow-up time point. Patients who experience ischemic events may require prolonged clopidogrel therapy, as with our patients who were not compliant, which perhaps influenced our trial's negative outcome. However, these rates were comparable to those in other trials with antithrombotic therapy (e.g., aspirin noncompliance in the WOEST trial: 33.5% [13], ADP receptor antagonist noncompliance in the PLATO [Platelet Inhibition and Patient Outcomes] trial: 22% [34], and clopidogrel nonadherence in the SECURITY

[Second Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy] trial: 34% [35]). Finally, duration of therapy may vary according to DES type; however, the study lacked the power to address specific treatment needs for different types of DES.

CONCLUSIONS

The ISAR-TRIPLE trial did not show that 6 weeks of triple therapy was superior to 6 months with regard to the net clinical outcome. These results suggest that physicians should weigh the trade-off between ischemic and bleeding risk when choosing the shorter or longer duration of triple therapy.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Nikolaus Sarafoff, Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Ludwig Maximilians Universität München, Marchioninistrasse 15, 81377 München, Germany. E-mail: n.sarafoff@gmail.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Antithrombotic therapy in patients with indications for oral anticoagulation undergoing implantation of drug-eluting stents is problematic. The optimum duration of triple therapy with 2 antiplatelet drugs plus an anticoagulant has not been established and may differ on the basis of individual patient, stent, and drug characteristics. A shorter (6-week) course of triple therapy was not superior to a longer (6-month) course when both major bleeding and ischemic events were considered.

TRANSLATIONAL OUTLOOK: Future studies should delineate the duration of therapy as a function of patient characteristics; number, location, and types of stents; and distinguishing features of platelet inhibitor and anticoagulant drug combinations used.

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KEY WORDS aspirin, atrial fibrillation, clopidogrel, percutaneous coronary intervention, vitamin K antagonist

APPENDIX For supplemental tables and figures, please see the online version of this article.