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Duration of Dual Antiplatelet Therapy and Outcomes After Coronary Stenting With the Genous™ Bio-engineered R Stent™ in Patients From the e-HEALING Registry

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Objective: We investigated the relation between duration of dual antiplatelet therapy (DAPT) and clinical outcomes up to 12 months after Genous™ endothelial progenitor cell capturing R stent™ placement in patients from the e-HEALING registry. Background: Cessation of (DAPT) has been shown to be associated with the occurrence of stent thrombosis (ST). After Genous placement, 1 month of DAPT is recommended. Methods: Patients were analyzed according to continuation or discontinuation of DAPT at a 30-day and 6-month landmark, excluding patients with events before the landmark. Each landmark was a new baseline, and outcomes were followed up to 12 months after stenting. The main outcome for our current analysis was target vessel failure (TVF), defined as target vessel-related cardiac death or myocardial infarction and target vessel revascularization. Secondary outcomes included ST. (Un)adjusted hazard ratios (HR) for TVF were calculated with Cox regression. Results: No difference was observed in the incidence of TVF [HR: 1.03; 95% confidence intervals (CI): 0.65–1.65, $P = 0.89$] in patients continuing DAPT ($n = 4,249$) at 30 days versus patients stopped ($n = 309$), and HR: 0.82 (95% CI: 0.55–1.23, $P = 0.34$) in patients continuing DAPT ($n = 2,654$) at 6 months versus patients stopped [$n = 1,408$] DAPT). Furthermore, no differences were observed in ST. Even after addition of identified independent predictors for TVF, adjusted TVF hazards were comparable. Conclusions: In a post-hoc analysis of e-HEALING, duration of DAPT was not associated with the occurrence of the outcomes TVF or ST. The Genous stent may be an attractive treatment especially in patients at increased risk for (temporary) cessation of DAPT or bleeding. © 2011 Wiley Periodicals, Inc.

Key words: e-HEALING; Genous™; EPC capturing R stent™; dual antiplatelet therapy

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INTRODUCTION

The use of drug-eluting stents (DES) is associated with a reduction in restenosis and the need for repeat revascularization, when compared with bare-metal stenting [1,2]. This reduction in restenosis is accomplished by impeding smooth muscle cell migration and proliferation through the release of antiproliferative drugs. Accompanying the effects of these drugs is the impairment of the normal healing process of the injured arterial wall by delaying the formation of a functional endothelial layer over the stent, predisposing patients for the occurrence of (late) stent thrombosis (ST) [3]. The incidence of late ST has been estimated to be 0.4–0.6% annually up to 4 years after DES implantation [4]. Dual antiplatelet therapy (DAPT) is recommended after DES placement to reduce the incidence of ST. Cessation of DAPT has been shown to be associated with the occurrence of ST in bare-metal stent (BMS) and DES, however, the risk was significantly higher in patients who had received a DES [5]. Therefore, the current percutaneous coronary intervention (PCI) guidelines recommend at least 6 (European guidelines) or 12 months (American guidelines) of DAPT after DES placement [6,7]. Complicating the use of DES is the unknown optimal duration of DAPT. In a recent report, continuation of DAPT longer than twelve months after stent implantation was not more effective than aspirin monotherapy [8].

The Genous endothelial progenitor cell (EPC) capturing stent promotes endothelialization of the stent struts and vessel segments, thereby potentially inhibiting smooth muscle cell proliferation and preventing restenosis and ST. Only one month of DAPT is recommended after Genous placement, and the HEALING studies have shown the safety and efficacy of this stent [9,10]. It may therefore be an attractive treatment in patients at increased risk for (temporary) cessation of DAPT. However, the duration of DAPT with Genous has not been investigated in a large cohort of patients. e-HEALING was a multicenter, prospective, worldwide, post-approval registry aimed at collecting data on approximately 5,000 patients treated with the Genous stent during routine non-urgent PCI. In this analysis, we investigated the relation between duration of DAPT and clinical outcomes in patients enrolled in the e-HEALING registry.

METHODS

Study Design

The study design, data collection and management, and quality control have been described previously [11]. In brief, the e-HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) was a worldwide, multicenter post-marketing registry. Approximately 5,000 patients were included between October 2005 and October 2007 from 144 centers in Europe, Asia/Pacific, Middle East, Africa, and Latin America. The list of sites and investigators can be found in the main manuscript. The local medical ethics committees approved the study protocol at sites at which such approval was legally required and written informed consent was obtained.

Device Description

The Genous stent comprises a covalently coupled polysaccharide matrix coating with monoclonal murine anti-human CD34+ antibodies on the abluminal stent surface, attached to a 316L stainless steel stent (Genous™ Bio-engineered R stent™, OrbusNeich Medical Technologies, Fort Lauderdale, FL).

Study Population and Procedures

Patients who underwent non-urgent PCI with at least one lesion suitable for stenting with a Genous stent (diameter 2.50–4.00 mm, length 9–33 mm) in accordance with the instructions for use were eligible for the e-HEALING registry. In case of multiple lesions, all lesions were preferably treated with a Genous stent but not mandatory per protocol. The indication for PCI was left at the discretion of the operator. A recommendation to receive at least 2 weeks of statin therapy before PCI was given. DAPT for at least one month post-procedure was recommended, but the actual duration of DAPT was at the discretion of the investigator. Aspirin was given indefinitely. The use of other concomitant medication was also left at the discretion of the treating physician. Medication use, including DAPT, was recorded at the time of study visit at 30 days, 6 months, and 12 months.

Outcomes

The main outcome for our current analysis was target vessel failure (TVF) up to 12 months after the index procedure, defined as the composite of cardiac death or myocardial infarction (MI) unless unequivocally attributable to a non-target vessel and target vessel revascularization (TVR). Secondary outcomes were the composite of cardiac death or MI, and the individual outcomes cardiac death, MI, ST according to the definitions of the academic research consortium (ARC) [12], and bleeding. A non-Q-wave MI was defined as an elevation of post-procedure CK levels above two times the upper limit of normal (ULN) in the absence

of pathological Q-waves. A Q-wave MI was defined as the development of new, pathological Q-waves in two or more continuous leads with an elevation of CK-MB above the ULN. TVR was defined as the repeat revascularization of any segment of the major coronary artery treated at the index procedure. Finally, bleeding was considered major when it led to death or permanent disability, suspected or proven intracranial, produced a fall in hemoglobin >3 mmol/l, led to transfusion of two or more units of whole blood of packed cells, or led to peripheral vascular surgery. All other bleeding were considered as minor. All outcome events were assessed at discharge of initial hospitalization, at 30 days, at 6 months and at 12 months. The following events were adjudicated with full source verification by an independent clinical event committee whose members did not participate in the study: death, MI, TVR, and ST.

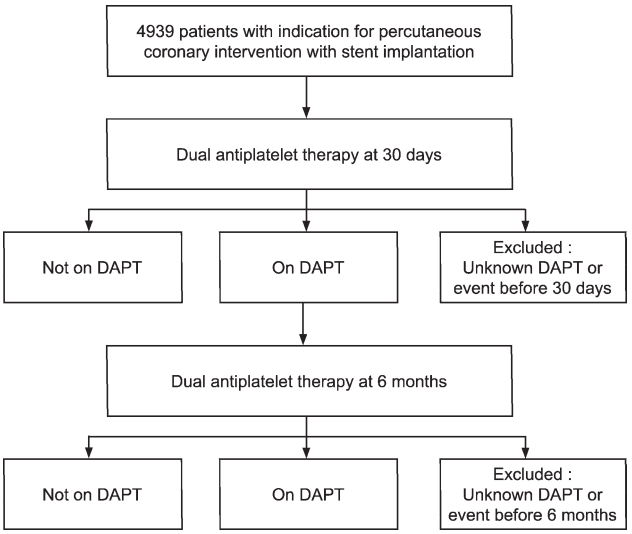

Fig. 1. Flow chart for dual antiplatelet therapy analysis.

Statistical Analysis

The overarching hypothesis of our current analysis was that duration of DAPT was not related to the incidence of clinical outcomes. We performed two analyses, one using predefined landmarks and one using an extended Cox model including DAPT as a time-dependent variable. We used the following two landmarks for our landmark analysis: DAPT at 30 days and DAPT at 6 months. For each landmark, we compared patients who continued DAPT at this landmark with patients who stopped DAPT before this landmark. Patients who endured an event (TVF) before the landmark and patients with unknown DAPT adherence were excluded from our analyses (Fig. 1). Each landmark was used as a new baseline, and outcomes were followed up to 12-months after Genous placement. Baseline, angiographic, and procedural characteristics were compared with the chi-square test in case of categorical variables or with the Student T-test (normal distribution) or the Wilcoxon rank-sum test (skewed distribution) in case of continuous variables. Cumulative event rates were estimated with the Kaplan-Meier method and compared with a log-rank test. Patients were censored at 12 months or at the date of last known follow-up, whichever came first. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated with Cox proportional-hazards models. We used two sets of models for the main outcome TVF: univariable models and multivariable with adjustment for independent predictors of TVF. These predictors were identified by backwards selection of baseline, angiographic and procedural variables, a $P < 0.1$ by the Likelihood ratio test was deemed significant.

In the extended Cox model, DAPT was entered as a time-dependent variable. In case of discontinuation of DAPT, we assumed that there was no restart until the end of follow-up. In this time-dependent analysis, we included all patients with known DAPT data. We believe that this assumption is close to reality because an important indication for DAPT is MI or stent placement. If a patient endures one of these events it is already counted as an outcome and the patient is censored for further outcomes.

Because some patients included in e-HEALING received other stents (DES or BMS) besides Genous, the duration of DAPT could also be influenced by these stents. We separately analyzed patients treated solely with Genous, and no heterogeneity was observed in outcomes.

Statistical analyses were performed at the Academic Medical Center, University of Amsterdam, The Netherlands.

RESULTS

Patients

Of the 4,996 patients entered in the e-HEALING registry, 52 patients were excluded because of missing procedure-related data ($n = 16$), no Genous stent was placed or Genous placement was unknown ($n = 36$), or missing follow-up data ($n = 5$). DAPT adherence at 30 days was known for 4,558 patients and for 4,062 patients at 6 months. Regarding TVF occurring before the landmarks, 85 and 273 TVF events were observed before the 30-day and 6-month landmark respectively. These patients were excluded from the respective landmark analyses. The baseline characteristics of the patients included in the four study groups are shown in Table I. Overall, there were significant differences in

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TABLE I. Baseline Characteristics

	Patient on DAPT at 30 days					Patient on DAPT at 6 months				
	Continued		Stopped			Continued		Stopped		
Characteristic	(n = 4,249)		(n = 309)		P value	(n = 2,654)		(n = 1,408)		P value
Demographics—no./total no. (%)										
Age—median (IQR)	63	(54-71)	69	(58-76)	<0.001	62	(53-70)	66	(57-73)	<0.001
Male gender	3,367/4,248	(79.3%)	223/309	(72.2%)	<0.01	2,162/2,653	(81.5%)	1,055/1,408	(74.9%)	<0.001
BMI—mean (SD)	27.3	(4.8)	27.5	(4.1)	0.57	27.4	(5.1)	27.1	(4.2)	0.08
Diabetes	1,062/4,249	(25.0%)	68/309	(22.0%)	0.24	642/2,654	(24.2%)	333/1,408	(23.7%)	0.70
Insulin dependent	231/4,249	(5.4%)	19/309	(6.1%)	0.27	117/2,654	(4.4%)	88/1,408	(6.3%)	0.01
Hypertension	2,926/4,243	(69.0%)	205/307	(66.8%)	0.43	1,837/2,651	(69.3%)	946/1,404	(67.4%)	0.21
Hypercholesterolemia	3,174/4,235	(74.9%)	212/309	(68.6%)	0.01	2,005/2,648	(75.7%)	1,028/1,402	(73.3%)	0.10
Current smoker	1,089/4,249	(25.6%)	52/309	(16.8%)	<0.01	736/2,654	(27.7%)	305/1,408	(21.7%)	<0.001
Family history of myocardial infarction	1,179/4,238	(27.8%)	87/309	(28.4%)	<0.001	738/2,645	(27.9%)	400/1,404	(28.5%)	<0.001
Congestive heart failure	136/4,227	(3.2%)	19/306	(6.2%)	<0.01	73/2,640	(2.7%)	62/1,397	(4.4%)	0.01
History—no./total no. (%)										
Myocardial infarction	1,571/4,249	(37.0%)	101/309	(32.7%)	0.13	967/2,654	(36.4%)	509/1,408	(36.2%)	0.86
Percutaneous coronary intervention	816/4,249	(19.2%)	57/309	(18.4%)	0.74	435/2,654	(16.4%)	313/1,408	(22.2%)	<0.001
Coronary artery bypass grafting	252/4,249	(5.9%)	25/309	(8.1%)	0.13	148/2,654	(5.6%)	95/1,408	(6.7%)	0.13
Prior stroke	242/4,234	(5.7%)	19/307	(6.2%)	0.73	146/2,648	(5.5%)	84/1,397	(6.0%)	0.51
Indication for PCI—no. /total no. (%)					0.43					<0.001
Elective	1,968/4,249	(46.3%)	147/309	(47.6%)		1,142/2,654	(43.0%)	720/1,408	(51.1%)	
ACS	1,915/4,249	(45.1%)	142/309	(46.0%)		1,281/2,654	(48.3%)	552/1,408	(39.2%)	
Other/unknown	366/4,249	(8.6%)	20/309	(6.5%)		231/2,654	(8.7%)	136/1,408	(9.7%)	
Prior medication use—no./total no. (%)										
Aspirin	3,528/4,249	(83.0%)	261/309	(84.5%)	0.52	2,224/2,654	(83.8%)	1,176/1,408	(83.5%)	0.82
Clopidogrel	2,525/4,249	(59.4%)	158/309	(51.1%)	<0.01	1,601/2,654	(60.3%)	800/1,408	(56.8%)	0.03

ACS : acute coronary syndrome, BMI : body mass index, DAPT : dual antiplatelet therapy, IQR : interquartile range, PCI : percutaneous coronary intervention, SD : standard deviation

demographics and risk factors for coronary artery disease between study groups. Patients who continued DAPT at 6 months significantly more often had an acute coronary syndrome as the indication for the index PCI, compared with patients who stopped before 6 months.

Angiographic and Procedural Characteristics

Detailed angiographic and procedural characteristics are shown in Table II. Patients who continued DAPT at 30 days and 6 months showed grade 3 TIMI flow less often at baseline and the end of the procedure and were less often treated for a B2 or C lesion than DAPT stopped patients.

Outcomes

No difference was observed in the incidence of the main outcome TVF (6.5% in patients continuing DAPT at 30 days versus 6.3% in patients stopped, $P = 0.89$, and 2.4% in patients continuing DAPT at 6 months versus 2.9% in patients who stopped, $P = 0.34$). Furthermore, no significant differences were observed in the composite outcome cardiac death or MI and the individual outcomes cardiac death, MI, definite or probable ST and definite or probable or possible ST. Regarding bleeding, a significant higher bleeding rate was observed in patients who stopped DAPT at 30 days. No difference was observed between patients who continued or stopped DAPT at 6 months. Clinical outcomes according to DAPT at 30 days are shown in Table III and according to DAPT at 6 months in Table IV. Kaplan-Meier curves of the outcome TVF are shown in Fig. 2.

Regarding the main outcome TVF, comparable hazards were observed at the 30-day landmark (HR: 1.03; 95% CI: 0.65–1.65, $P = 0.89$) and the 6-month landmark (HR: 0.82; 95% CI: 0.55–1.23, $P = 0.34$) when comparing patients who continued DAPT with patients who stopped. These HR were unaffected, overlapping equivalence, after adjustment for other independent predictors of the main outcome. The following variables were identified as independent predictors for TVF: age, insulin-requiring diabetes mellitus, previous PCI, history of stroke, indication for PCI, mean reference vessel diameter, mean lesion length, at least one restenosis, at least one B2 or C lesion treated and at least one lesion with post-procedure TIMI 0-2 flow. Unadjusted and adjusted HRs for TVF are shown in Table V.

In the time-dependent analysis (Table V), 4,529 patients were included. No difference in TVF was observed when comparing patients who continued DAPT with patients who discontinued DAPT after adjustment for relevant predictors for TVF (HR: 1.00; 95% CI: 0.75–1.31, $P = 0.97$).

In exploratory landmark analyses we calculated adjusted HRs for the main outcome TVF in patients undergoing elective PCI or PCI for acute coronary syndrome (ACS). In the elective PCI subgroup, comparable TVF hazards were observed at the 30-day landmark (HR: 1.25; 95% CI: 0.61–2.57, $P = 0.55$) and 6-month landmark (HR: 0.63; 95% CI: 0.36–1.13, $P = 0.12$) when comparing continuing with stopped patients. These HRs were respectively 1.21 (95% CI: 0.61–2.39, $P = 0.59$) and 1.72 (95% CI: 0.84–3.55, $P = 0.14$) in patients undergoing PCI for ACS.

DISCUSSION

Our current analysis from the multicenter, prospective, worldwide e-HEALING registry of patients stented with Genous during PCI shows that the duration of DAPT after stent placement was not associated with clinical outcomes. The hazard for TVF was comparable in patients continuing DAPT or patients who stopped DAPT at 30 days or 6 months, even after adjustment for independent predictors for TVF. DAPT was not a predictor for TVF in the extended Cox model. Furthermore, we did not observe significant differences in the outcome ST in patients continuing DAPT or patients who stopped DAPT at 30 days or 6 months.

Previous Studies

The optimal duration of DAPT after DES placement is a topic for discussion. In the PREMIER registry, DES-treated MI patients who stopped DAPT at 30 days were compared with patients who continued DAPT. Prematurely stopping of DAPT was associated with subsequent mortality in the following 11 months [13]. However, ST rates were not reported, and the authors noted that the adverse prognosis associated with discontinuing DAPT may also partly be explained by noncompliance as a marker for overall medical noncompliance. This overall medical noncompliance may have accounted for some of the mortality. The association between discontinuation of DAPT and subsequent ST with DES is complicated by studies that show that this association is the strongest within the first 6 months after PCI, not thereafter [14,15]. However, another study showed that long-term DAPT was associated with reduced death or MI [16]. The main limitation of these aforementioned studies is the nonrandomized design.

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TABLE II. Baseline angiographic and procedural characteristics

	Patient on DAPT at 30 days					Patient on DAPT at 6 months				
Characteristic	Continued		Stopped		*P* value	Continued		Stopped		*P* value
Patient characteristics	4,249		309			2,654		1,408		
Target lesion coronary artery										
Multivessel PCI	699/4,238	(16.5%)	47/308	(15.1%)	0.57	458/2,649	(17.3%)	204/1,402	(14.6%)	0.03
Bypass graft	39/4,238	(0.9%)	4/308	(1.3%)	0.51	28/2,649	(1.1%)	10/1,402	(0.7%)	0.28
Left main	75/4,238	(1.8%)	3/308	(1.0%)	0.30	52/2,649	(2.0%)	15/1,402	(1.1%)	0.03
Lesions per patient—mean (SD)	1.3	(0.6)	1.4	(0.7)	0.34	1.4	(0.7)	1.3	(0.6)	0.40
Lesion characteristics	5,644		422			3,557		1,863		
Lesion type—no. /total no. (%)					<0.001					0.03
De novo	5,527/5,644	(97.9%)	402/422	(95.3%)		3,495/3,557	(98.3%)	1,814/1,863	(97.4%)	
Restenotic	117/5,644	(2.1%)	20/422	(4.7%)		62/3,557	(1.7%)	49/1,863	(2.6%)	
Bifurcation lesion	548/5,644	(9.7%)	46/422	(10.9%)	0.43	328/3,557	(9.2%)	204/1,863	(11.0%)	0.04
Lesion Classification—no. /total no. (%)					<0.001					<0.001
A	927/5,644	(16.4%)	36/422	(8.5%)		650/3,557	(18.3%)	225/1,863	(12.1%)	
B1	2,013/5,644	(35.7%)	130/422	(30.8%)		1,254/3,557	(35.3%)	669/1,863	(35.9%)	
B2	1,644/5,644	(29.1%)	171/422	(40.5%)		1,014/3,557	(28.5%)	589/1,863	(31.6%)	
C	1,060/5,644	(18.8%)	85/422	(20.1%)		639/3,557	(18.0%)	380/1,863	(20.4%)	
Baseline angiographic findings—mean (SD)										
Lesion length—mm	16.7	(8.4)	17.2	(10.0)	0.21	17.1	(8.7)	16.3	(8.3)	<0.01
Reference-vessel diameter—mm	3.0	(0.4)	3.1	(0.4)	0.001	3.0	(0.4)	3.0	(0.4)	<0.001
Stenosis—% of vessel diameter	85	(12)	86	(10)	<0.01	85	(12)	85	(12)	0.15
Baseline TIMI flow grade—no. /total no. (%)					<0.001					<0.001
Grade 0	575/5,644	(10.2%)	33/422	(7.8%)		359/3,557	(10.1%)	188/1,863	(10.1%)	
Grade 1	606/5,644	(10.7%)	30/422	(7.1%)		457/3,557	(12.8%)	129/1,863	(6.9%)	
Grade 2	1,071/5,644	(19.0%)	41/422	(9.7%)		816/3,557	(22.9%)	214/1,863	(11.5%)	
Grade 3	3,392/5,644	(60.1%)	318/422	(75.4%)		1,925/3,557	(54.1%)	1,332/1,863	(71.5%)	
Stent use										
Stents per lesion—mean (SD)	1.1	(0.4)	1.1	(0.4)	0.58	1.1	(0.4)	1.1	(0.4)	0.11
Type of stent placed					0.16					<0.001
Genous only	4,827/5,644	(85.5%)	369/422	(87.4%)		2,985/3,557	(83.9%)	1,651/1,863	(88.6%)	
Genous and/or other	711/5,644	(12.6%)	43/422	(10.2%)		512/3,557	(14.4%)	177/1,863	(9.5%)	
No or unknown	106/5,644	(1.9%)	10/422	(2.4%)		60/3,557	(1.7%)	35/1,863	(1.9%)	
Direct stenting attempted	2,188/5,644	(38.4%)	150/422	(35.5%)	0.24	1,447/3,557	(40.7%)	654/1,863	(35.1%)	<0.001
Final angiographic findings—mean (SD)										
Reference-vessel diameter—mm	3.1	(0.4)	3.1	(0.4)	<0.01	3.0	(0.4)	3.1	(0.4)	<0.001
Stenosis—% of vessel diameter	5	(15)	3	(10)	<0.01	6	(17)	3	(8)	<0.001
Final TIMI flow grade—no. /total no. (%)					<0.001					<0.001
Grade 0	194/5,644	(3.4%)	2/422	(0.5%)		185/3,557	(5.2%)	8/1,863	(0.4%)	
Grade 1	32/5,644	(0.6%)	2/422	(0.5%)		24/3,557	(0.7%)	6/1,863	(0.3%)	
Grade 2	199/5,644	(3.5%)	3/422	(0.7%)		166/3,557	(4.7%)	31/1,863	(1.7%)	
Grade 3	5,219/5,644	(92.5%)	415/422	(98.3%)		3,182/3,557	(89.5%)	1,906/1,863	(97.6%)	

PCI = percutaneous coronary intervention, SD = standard deviation.
Angiographic variables.

TABLE III. Outcomes Between 1 and 6 Months According to DAPT at 30 Days

	Patient on DAPT at 30 days					
	Continued (n = 4,249)		Stopped (n = 309)			
Outcome	No. (%)[b]				Hazard Ratio (95% CI)	P value[a]
Composite outcomes						
Target vessel failure	268/4,249	(6.5%)	19/309	(6.3%)	1.03 (0.65–1.65)	0.89
Cardiac death or MI	63/4,245	(1.5%)	6/309	(2.0%)	0.77 (0.33–1.78)	0.54
Individual outcomes						
Cardiac death	40/4,249	(1.0%)	4/309	(1.3%)	0.73 (0.26–2.05)	0.55
MI	25/4,245	(0.6%)	2/309	(0.6%)	0.91 (0.22–3.86)	0.90
Target-vessel revascularization	227/4,249	(5.5%)	15/309	(5.0%)	1.11 (0.66–1.87)	0.70
ARC stent thrombosis						
Definite or probable ST	9/4,248	(0.2%)	2/309	(0.6%)	0.33 (0.07–1.52)	0.16
Definite/probable/possible ST	44/4,248	(1.1%)	6/309	(2.0%)	0.54 (0.23–1.26)	0.15
Bleeding	9/4,213	(0.2%)	6/303	(2.0%)	0.11 (0.04–0.30)	<0.001

[a]Derived from Cox proportional-hazards model.
[b]Kaplan-Meier estimates.
Of the nine bleeding events in the continued group and the six in the stopped group, respectively three and four were major bleedingMI = myocardial infarction; ST = stent thrombosis.

TABLE IV. Outcomes between 6 and 12 months according to DAPT at 6 months

	Patient on DAPT at 6 months					
	Continued (n = 2,654)		Stopped (n = 1,408)			
Outcome	No. (%)[b]				Hazard Ratio (95% CI)	P value[a]
Composite outcomes						
Target vessel failure	62/2,654	(2.4%)	40/1,408	(2.9%)	0.82 (0.55–1.23)	0.34
Cardiac death or MI	14/2,653	(0.5%)	11/1,404	(0.8%)	0.68 (0.31–1.49)	0.33
Individual outcomes						
Cardiac death	10/2,654	(0.4%)	8/1,408	(0.6%)	0.67 (0.26–1.69)	0.39
MI	4/2,653	(0.2%)	4/1,404	(0.3%)	0.53 (0.13–2.12)	0.37
Target-vessel revascularization	51/2,654	(2.0%)	32/1,408	(2.3%)	0.85 (0.54–1.32)	0.46
ARC stent thrombosis						
Definite or probable ST	1/2,653	(0.0%)	1/1,408	(0.1%)	0.53 (0.03–8.60)	0.66
Definite/probable/possible ST	11/2,653	(0.4%)	8/1,408	(0.6%)	0.74 (0.30–1.83)	0.51
Bleeding	1/2,639	(0.1%)	2/1,380	(0.1%)	0.26 (0.02 -2.83)	0.27

[a]Derived from Cox proportional-hazards model
[b]Kaplan-Meier estimates
Of the 1 bleeding event in the continued group and the 2 in the stopped group, respectively 0 and 2 were major bleeding
MI : myocardial infarction, ST : stent thrombosis

DAPT Recommendation and HEALING Studies

After Genous stent placement, only 1 month of DAPT is recommended. The safety of this recommendation has been investigated previously in the HEALING studies where all patients received one month of DAPT. In the HEALING—First In Man registry, including 16 patients treated with the Genous stent, no cases of ST were observed and a major adverse cardiac and cerebrovascular event (MACCE) rate of 6.3% was observed at 9 months of follow-up [9]. In the following HEALING-II registry, 63 patients were treated with a Genous stent [10]. At 18-month follow-up, no (sub)acute or late angiographic ST occurred. The 18-month MACE rate was 7.9%. Our current report extends the current body of knowledge with comparable outcomes and low ST rates in a large cohort of patients who continued or stopped DAPT at 1 or 6 months.

Bleeding

The incidence of bleeding was significantly higher in patients after stopping DAPT compared with patients who continued DAPT. In view of the lack of a biological rationale, this finding is suggestive for the selection of patients with a high bleeding risk who consequently stopped DAPT. Bleeding complications, together with patient compliance, surgery, allergy to clopidogrel and costs have previously been identified as important predictors for discontinuation of DAPT [17]. Because of the low bleeding event rate in e-HEALING, we were

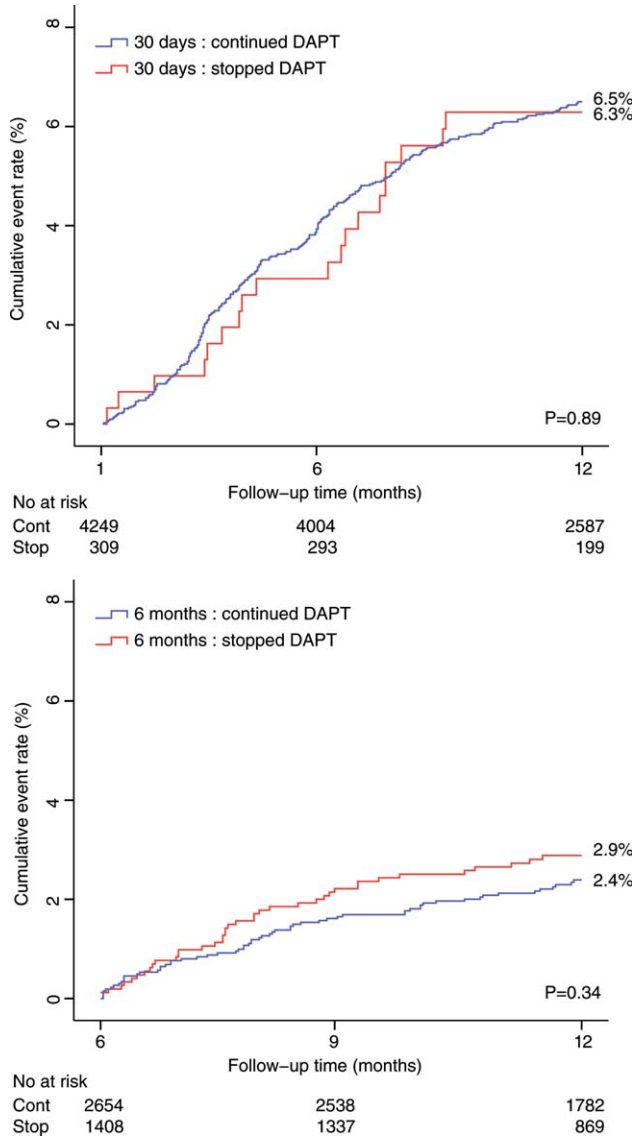

Fig. 2. Kaplan-Meier curves of target vessel failure. Shown is the outcomes target vessel failure (composite of cardiac death or myocardial infarction unless unequivocally attributable to a non-target vessel and target vessel revascularization). *P* value by the log-rank test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

not able to compare continuation with discontinuation of DAPT with adjustments for baseline risk or relevant predictors of bleeding. A shorter duration of DAPT is potentially associated with decreased bleeding, warranting further investigation.

Acute Coronary Syndromes

Despite the recommendation of only one month of DAPT, many patients were on DAPT for longer than one month. We postulate that this is largely driven by guideline recommendation of prolonged DAPT in patients presenting with ACS as the indication for PCI or by patients who received a Genous and a DES. Our results show that significantly more ACS patients continued DAPT at the 6-month landmark. However, in exploratory analyses, we did not observe heterogeneity in the association DAPT duration and outcomes between different indications for PCI, including ACS. Moreover, ST rates were too low. Further research is required for definite conclusions regarding DAPT use in ACS patients treated with Genous.

TABLE V. Unadjusted and adjusted hazard ratios for target vessel failure

Outcome target vessel failure	Hazard Ratio (95% CI)	*P* value
DAPT at 30 days (continued compared with stopped)		
Unadjusted	1.03 (0.65–1.65)	0.89
Adjusted for predictors of TVF[a]	1.21 (0.75–1.96)	0.44
DAPT at 6 months (continued compared with stopped)		
Unadjusted	0.82 (0.55–1.23)	0.34
Adjusted for predictors of TVF[a]	0.85 (0.56–1.29)	0.44
Time extended Cox model (continued vs. stopped)		
Unadjusted	0.87 (0.67–1.14)	0.30
Adjusted for predictors of TVF[a]	1.00 (0.75–1.31)	0.97

[a]Adjusted for age, insulin-requiring diabetes mellitus, previous PCI, history of stroke, indication for PCI, mean reference vessel diameter, mean lesion length, minimal 1 restenosis, minimal 1 B2 or C lesion treated, minimal 1 bifurcation treated and minimal 1 lesion with post-procedure TIMI 0-2 flow.

Clinical Implications

It has been shown previously that early discontinuation of DAPT is associated with the occurrence of ST after DES placement [18,19]. This finding is of paramount importance in patients with a low therapeutic compliance or expected (coronary artery bypass) surgery. Our current results implicate that the recommendation of one month of DAPT is safe and effective. This finding, together with the relatively low event rates observed in the e-HEALING registry make the Genous stent an attractive treatment option especially in patients with an anticipated (temporary) cessation of DAPT or patients at an increased bleeding risk [11]. However, we recently described the outcomes of the TRIAS HR trial, in which patients with lesions at high-risk for restenosis were randomized to Genous or DES [20]. High-risk lesions were defined as a lesion with a length of $\geq$20 mm or reference vessel diameter of $\leq$2.8 mm, a chronic coronary artery occlusion or any lesion in a diabetic patient. In this trial, non-inferiority of Genous compared with DES with regards to TVF could not be established. This was mainly driven by higher TLR rates with Genous. The trial was underpowered to analyze the relation between DAPT and

ST, thus further research is required to weigh the potential benefit of Genous in terms of ST with the potential higher risk of TLR in these patients. Moreover, although low event rates with Genous are observed in the e-HEALING registry, a randomized comparison between Genous and BMS placement is currently not available. If the safety of Genous is accompanied by more efficacy compared with BMS is currently being investigated in the ongoing TRIAS low risk trial [21].

Limitations

Some limitations of our current analysis deserve mentioning. First, the patients in the e-HEALING registry were not randomized to different durations of DAPT. Therefore, the study groups may not be directly comparable and we cannot rule out the possibility that unmeasured confounders could have affected our results. However, despite the adjustment for independent predictors in Cox proportional-hazards models, the unadjusted and adjusted HR is our analyses were not affected. Second, underreporting of adverse events is a potential important shortcoming of all large registries. This study was organized with a comprehensive data-management plan that included frequent monitoring of all participating sites and full event verification designed to minimize the effects of this potential event underreporting. Third, the main outcome included repeat revascularization. We were not able to differentiate repeat revascularization for cardiac biomarker negative unstable angina from revascularization for restenosis. While the former is mainly due to plaque rupture and superimposed thrombus formation, the latter is due to intimal hyperplasia. Consequently, DAPT potentially influences only a part of this outcome. Finally, given the low event rates for ST and bleeding, our findings require confirmation in larger (randomized) trials.

CONCLUSION

In a post-hoc analysis of the e-HEALING registry of patients undergoing PCI with Genous stent placement, the duration of DAPT was not associated with the occurrence of the outcomes TVF or ST. The Genous stent may be an attractive stents especially in patients at increased risk for (temporary) cessation of DAPT or patients at an increased bleeding risk.

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