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Drug eluting stent implantation in patients requiring concomitant vitamin K antagonist therapy. One-year outcome of the worldwide e-SELECT registry ☆

Manel Sabaté [a,*], Salvatore Brugaletta [a], Alexandre Abizaid [b], Adrian Banning [c], Antonio Bartorelli [d], Vladimír Džavík [e], Stephen Ellis [f], David Holmes [g], Runlin Gao [h], Myung Ho Jeong [i], Victor Legrand [j], Franz-Josef Neumann [k], Maria Nyakern [l], Christian Spaulding [m], Hans-Peter Stoll [l], Stephen Worthley [n], Philip Urban [o] for the e-SELECT investigators

[a] Hospital Clinic, Barcelona, Spain
[b] Instituto Dante Pazzanese de Cardiologia, Sao Paolo, Brazil
[c] John Radcliffe Hospital, Oxford, United Kingdom
[d] Centro Cardiologico Monzino, IRCCS, University of Milan, Milan, Italy
[e] Peter Munk Cardiac Centre, University Health Network, Toronto, Canada
[f] Cleveland Clinic Foundation, Cleveland, USA
[g] Mayo Clinic, Rochester, MN, USA
[h] Cardiovascular Institute and Fu Wai Hospital, Beijing, China
[i] The Heart Center of Chonnam National University Hospital, GwangJu, Republic of Korea
[j] Centre Hospitalier Universitaire, Liège, Belgium
[k] Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany
[l] Cordis Clinical Research Europe, Waterloo, Belgium
[m] Department of Cardiology, Cochin Hospital, Paris Descartes University, Paris, France
[n] Cardiovascular Investigation Unit, Royal Adelaide Hospital, Adelaide, Australia
[o] La Tour Hospital, Geneva, Switzerland

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ABSTRACT

Background: Outcome of sirolimus-eluting stent (SES) in patients treated with an antivitamin K (VKA) agent before the PCI procedure is unknown.
Methods: A total of 7651 patients were selected among 15,147 recipients of SES, included in the worldwide e-SELECT registry, only from those centers which included at least one patient requiring VKA: 296 were pretreated with a VKA agent (VKA group), whereas 7355 patients from the same enrolling medical centers were not (NON-VKA group). The rates of 1) major adverse cardiac events (MACE), including all-cause deaths, myocardial infarction (MI) and target lesion revascularization, 2) stent thrombosis (ST) and 3) major bleeding (MB) in the 2 study groups were compared at 1, 6 and 12 months.
Results: The patients in VKA group were on average older as compared to those in NON-VKA group (67.7 ± 9.9 vs.62.9 ± 10.7, $P < 0.001$). The indications for pre-procedural anticoagulation were atrial fibrillation in 177 (59.8%), presence of a prosthetic valve in 21 (7.1%), embolization of cardiac origin in 17 (5.7%), pulmonary embolism or deep vein thrombosis in 17 (5.7%), and miscellaneous diagnoses in 64 (21.6%) patients. At 1 year, the rates of MACE and MB were higher in the VKA vs. the NON-VKA group (8.3% and 3% vs. 5.3% and 1.2%, $P < 0.04$and $P < 0.002$, respectively). The 1-year rates of definite and probable ST were remarkably low in both groups (0.38% vs. 1.1%, $p = 0.4$).
Conclusions: Selected patients anticoagulated with VKA agent may safely undergo SES implantation. Those patients may receive a variety of APT regimen at the cost of a moderate increased risk of MB.

1. Introduction

Among recipients of coronary artery drug eluting stents (DES), up to 10% are pretreated with warfarin or other oral antivitamin K (VKA) agents for the prevention of thromboembolism due to chronic atrial fibrillation, presence of a prosthetic valve, history of embolization of

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* Corresponding author at: Thorax Institute, Cardiology Department, Hospital Clinic, University of Barcelona, C/Villarroel 170, Barcelona, 08036, Spain. Tel./fax: +34 932270305.
E-mail address: masabate@clinic.ub.es (M. Sabaté).

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cardiac origin, or other indications for long-term, oral anticoagulation [1]. While a minority, these patients represent a particular challenge because of the complex antithrombotic regimen needed after a stent implantation procedure. Of note is that despite their high rate of comorbidity that can increase the probability of restenosis, these patients rarely receive a DES implantation, because of the associated need for long-term anti-platelet therapy with subsequent increase of bleeding events. However, no data are available for DES safety in patients under VKA regimen in a real world scenario [2,3].

The purpose of this sub-analysis of the e-SELECT registry was to compare the 1-year a) clinical outcomes, b) rates of hemorrhagic and thrombotic events, and c) compliance with dual APT among recipients of SES who were pre-treated versus non-pretreated with oral VKA agents.

2. Methods

2.1. Patient population

The e-SELECT worldwide registry, described in detail elsewhere [4], collected data between May 2006 and April 2008 in consecutive recipients of ≥1 CYPHER Select® or CYPHER Select® Plus (Cordis Corporation, Bridgewater, NJ) sirolimus-eluting stents (SES), implanted at 320 medical centers in 56 countries. The protocol, which specified very few exclusion criteria, allowed the implantation of SES for off-label indications, and all post-procedural medical managements, including antiplatelet therapy (APT), was according to usual local practices.

Among the 15,147 patients entered in e-SELECT registry, only patients included in those centers, which enrolled at least 1 patient pre-treated with VKA, were taken into account in order to avoid any pre-selection confounding factors, which may have occurred in those centers not enrolling any patients pre-treated with VKA. A total of 7651 patients were therefore selected and in particular we compared 296 patients pre-treated with a VKA agent (VKA group) with 7355 patients, enrolled at the same medical centers, not pre-treated with a VKA agent (NON-VKA group). All patients were followed at 1, 6 and 12 months after the SES implantation procedure. The ethics committee of each participating medical center approved the protocol and the patients granted their consent to participate in the registry after the PCI index procedure [1].

2.2. Data collection and management

The data collected by the e-SELECT registry include demographic information, general health and cardiovascular history, assessment of angina status, co-morbidity, lesion and procedure characteristics, procedural outcomes, measurements of cardiac enzymes and serum creatinine, pre- and post-procedural electrocardiogram, cardiac medications and anti-platelet therapy. Post-procedural clinical observations were performed up to 1 year of follow-up.

The data were collected electronically at each participating medical center, transferred to an independent data management organization (KIKA Medical, Nancy, France), and analyzed by an independent clinical research organization (Cardialysis, Rotterdam, the Netherlands). The overall consistency and accuracy of data collection were monitored by an independent organization (Covance, Princeton, NJ) in 20% of the overall sample, at 100 enrolling centers.

2.3. Endpoints of the e-SELECT registry

The primary objective of the registry was to analyze the rates of stent thrombosis (ST), as defined by the Academic Research Consortium (ARC) up to 1 year of follow-up [5]. In the present analysis, we also studied the 1-year rates of 1) major bleeding (MB), according to the STEEPLE definition (Appendix A) [6], 2) deaths and myocardial infarction (MI), and 3) major adverse cardiac events (MACE), a composite endpoint including a) all-cause deaths, b) MI, and c) percutaneous or surgical target lesion revascularization (TLR).

2.4. Study organization and supervision

A Steering Committee (Appendix B) planned the analysis of the registry, and presentations and publications of the results. A Clinical Event Committee (Appendix B) composed of interventional cardiologists not associated with the sponsor and not participants in the registry adjudicated all MACE, MB and acute, subacute, and late ST, by a systematic review of the data collection forms, and by review of the source documents, electrocardiograms and angiograms, when necessary.

2.5. Statistical analysis

The sample size calculations of e-SELECT, based on an estimated 3-year rate of definite or probable ST, using the ARC definitions, have been described previously [1,5]. Standard statistics were used for the description of patients, lesions and procedure characteristics, and of short- and long-term clinical observations. Continuous variables are presented as means ± standard deviations, and categorical variables as counts and percentages. Cumulative rates of ST and MB were calculated, using event-specific adjusted denominators. Missing values were not imputed. A two-side p-value < 0.05 was considered significant. All statistical analyses were performed, using the SAS software, version 9.1 or higher (SAS Institute, Cary, NC). The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Results

3.1. Baseline clinical and angiographic characteristics

The clinical characteristics of the 2 study groups are shown in Table 1. The VKA group was, on average, significantly older and exhibited higher rates of concomitant disorders compared with the NON-VKA group. The indications for pre-procedural anticoagulation in the VKA group were atrial fibrillation in 177 patients (59.8%), presence of a prosthetic valve in 21 (7.1%), embolization of cardiac origin in 17 (5.7%), pulmonary embolisms or deep vein thrombosis in 17 (5.7%), and other miscellaneous indications in 64 (21.6%) patients.

The angiographic and procedural characteristics of the 2 study groups are shown in Table 2. Except for slightly higher prevalence of restenotic and heavily calcified lesions in the VKA group, no noteworthy differences were observed.

3.2. Anticoagulation and antiplatelet therapy (Table 3)

The proportions of patients in each study group, who received single and dual APT and VKA agents before, during and after the SES procedure, and up to 1-year follow-up are shown in Table 3. In the VKA group, nearly 60% continued on anticoagulation throughout the 1-year follow-up. It is noteworthy that within this group 30% of patients also received pre-procedural dual APT. Thereafter, the proportions of patients treated with dual APT decreased to 87%, 75% and nearly 60% at 1, 6 and 12 months, respectively, after the index SES implant procedure. Conversely, in the NON-VKA group, nearly 100%, 95% and 80% of patients received dual APT at 1, 6 and 12 months,

Table 1
Baseline characteristics of patients pretreated (VKA group) versus patients untreated (NON-VKA group) with an antivitamin K agent.

	VKA group (n = 296)	NON-VKA group (n = 7355)	*P-value*
Age, year	67.7 ± 9.9	62.9 ± 10.7	<0.001
Men	228 (77)	5510 (75)	0.45
Body mass index ≥ 30	90 (30.4)	1924 (26.2)	0.11
History of:			
Myocardial infarction	128 (43.2)	2500 (34.0)	<0.001
Congestive heart failure	56 (18.9)	288 (3.9)	<0.001
Percutaneous coronary intervention	130 (43.9)	2592 (35.2)	0.003
Coronary artery bypass graft surgery	56 (18.9)	762 (10.4)	0.001
Diabetes	97 (32.8)	2189 (29.8)	0.27
Insulin-dependent	33 (11.1)	642 (8.7)	0.36
Hypertension	232 (78.4)	5084 (69.1)	0.001
Hyperlipidemia	219 (74.0)	5334 (72.5)	0.64
Current and past smoking	160 (54.0)	4035 (54.9)	0.81
Peripheral vascular disease	44 (14.9)	532 (7.2)	<0.001
Cerebral vascular disease	44 (14.9)	313 (4.3)	<0.001
Serum creatinine > 2.0 mg/dl	14 (5.2)	178 (2.7)	0.023
Chronic lung disease	24 (8.1)	311 (4.2)	0.003
Mean Charlson comorbidity index score	1.76 ± 1.66	1.10 ± 1.34	<0.001
Charlson index score ≥ 3	73 (24.7)	822 (11.2)	<0.001
Coronary arteries with >50% stenoses			
0	36 (12.2)	673 (9.2)	0.08
1	228 (77.0)	5569 (75.7)	0.63
2	29 (9.8)	998 (13.6)	0.07
3	3 (1.0)	112 (1.5)	0.63
4	0	3 (0.04)	1.00
			1.00
Left ventricular ejection fraction <30%	20 (8.1)	117 (1.9)	<0.001
Sinus rhythm	162 (60.5)	6428 (97.3)	<0.001

Values are means ± SD or numbers (%) of observations.

Table 2
Lesion and procedure characteristics in 296 patients treated (VKA group) versus 7355 patients untreated (NON-VKA group) with an antivitamin K agent.

	VKA group (n = 296 patients, 389 lesions, 462 stents)	NON-VKA group (n = 7355 patients, 9925 lesions, 11,803 stents)	*P-value*
Reference vessel diameter, mm[a]	2.93 ± 0.45	2.91 ± 0.46	0.39
Pre-procedural percent stenosis[a]	83.9 ± 12.8	84.5 ± 12.3	0.39
Lesion length, mm[a]	19.9 ± 12.5	19.9 ± 11.8	0.98
Target lesion types			
In native coronary artery	366 (94.3)	9696 (97.8)	<0.001
Restenotic[b]	74 (19.3)	1337 (13.6)	0.002
Length ≥ 20 mm[c]	166 (43.3)	4257 (43.3)	1.00
Heavily calcified[b]	28 (8.2)	376 (4.3)	0.002
Procedural characteristics			
Numbers per patient			
Vessels treated	1.2 ± 0.4	1.2 ± 0.4	0.29
Lesions treated	1.3 ± 0.6	1.3 ± 0.6	0.37
Stents implanted	1.6 ± 0.8	1.6 ± 0.9	0.41
Total stent length, mm			
Per lesion	24.6 ± 13.4	25.0 ± 13.3	0.62
Per patient	32.2 ± 20.8	33.7 ± 21.5	0.23
Direct stenting	144 (37.5)	3533 (35.9)	0.58
Pre-dilatation	240 (62.5)	6314 (64.1)	0.45
Post-dilatation	166 (37.6)	4586 (40.3)	0.17
Intravascular ultrasound imaging	18 (4.8)	277 (2.8)	<0.001
Duration of hospitalization (days)	3.7 ± 4.6	3.1 ± 3.2	0.002

Values are means ± SD, or numbers (%) of observation.
[a] Visual estimate.
[b] Calculated per lesion.
[c] Calculated per patient.

respectively, and very few patients were started on VKA after the index procedure.

3.3. Clinical outcomes, stent thrombosis and major bleeding (Table 4 and Fig. 1)

Among the 296 patients included in the VKA group, 1-, 6- and 12-month follow-ups were completed in 99.7%, 98.6% and 94.0% of the patients, respectively. Among the 7355 patients included in the NON-VKA group, follow-up was completed in 99.3%, 98.1% and 94.8% of the patients at 1-, 6- and 12-months, respectively.

The MACE rate was low in both study groups, but was significantly higher in the VKA than in the NON-VKA (8.3% vs. 5.3%, p = 0.04) group at 12 months follow-up (Fig. 1). Similarly, the rates of MB were low in both groups, though it was 2-fold higher at 1 month (1.0% vs. 0.5%, p = 0.19) and nearly 3-fold higher at 6 (2.1% vs. 0.8%, p = 0.036) and 12 months (3.0% vs. 1.2%, p = 0.002) in the VKA than in the NON-VKA group (Table 4).

The rates of ST as defined by ARC were remarkably low in both study groups. It is particularly noteworthy that, in the VKA group, the rate of acute and sub-acute ST was 0%, and that a single definite ST (0.38%) was observed at 1 year. In the NON-VKA group, the rates of acute, subacute and late definite/probable ST were also <1% (Table 5).

4. Discussion

Several observations can be made in this analysis. First, patients requiring VKA treatment had a higher prevalence of concomitant disorders (high Charlson comorbidity index) as compared to patients non-VKA treated, associated with a higher incidence of MACE during follow-up. Secondly, selected patients requiring VKA treatment can be safely treated with DES with relatively low incidence of stent thrombosis, despite a lower use of dual antiplatelet therapy compared with patients non-VKA treated. Finally, despite their lower use of dual APT, patients requiring VKA treatment do exhibit a higher rate of major bleeding when compared with patients without VKA treatment.

Previous studies in patients with atrial fibrillation under VKA treatment and receiving PCI have shown a MACE rate around 23% and 36% at 1 and 2 years follow-up [7–9]. This high rate of MACE has been explained by the high-risk profile of this population, with co-morbid conditions and subsequently high risk of ischemic and bleeding events [10–12]. The present sub-analysis from e-SELECT registry confirms this higher rate of MACE in VKA patients as compared to non-VKA patients, further supporting the role of baseline clinical profile (high Charlson index) in determining their worse clinical outcome [9]. It is noteworthy that whereas no differences in MACE or bleeding events were present between the two groups at 1-month follow-up, they became evident at 6 months, suggesting that these events need mid-time follow-up to accrue in patients VKA-treated. In contrast with previous studies, our analysis extended to a wider population, including patients under VKA-treatment not only for atrial fibrillation, but also for other clinical reasons (e.g. prosthetic valve).

In addition, it is important to note that the MACE rate in the VKA group was in our analysis consistently lower (8.3% at 1 year) as compared to previous reports [7,8]. It may be argued that use of SES in our population could have played a major role in this relatively low MACE rate. Previous reports indeed did include a heterogeneous population with regard to the drug-eluting stent implanted, having different late loss and therefore different MACE rates. In the study of Rogacka et al., for instance, only 59.2% were SES, 35.2% were paclitaxel-eluting stents and the rest were BMS. This resulted in a MACE and TLR rates of 19.7% and 12.7%, respectively, in the DES group [7]. Ruiz-Nodar

Table 3
Pre-, intra- and post-procedural anticoagulation and antiplatelet regimens in both study groups.

	VKA group	NON-VKA group	*P-value*
Preprocedural	(n = 296)	(n = 7355)	
Antiplatelet regimens			
None	95 (32.4)	692 (9.4)	<0.001
Aspirin or thienopyridine only	111 (37.9)	2539 (34.7)	0.29
Dual regimen	87 (29.4)	4082 (55.8)	<0.001
VKA	296 (100)	0	na
Intraprocedural	(n = 294)	(n = 7340)	
Antiplatelet regimens			
Aspirin or thienopyridine only	46 (15.7)	729 (10.0)	0.003
Dual regimen	227 (77.5)	5982 (81.7)	0.08
Glycoprotein IIb/IIIa inhibitor	47 (16.0)	1157 (15.8)	0.935
Unfractionated or low-molecular heparin	272 (92.5)	6700 (91.3)	0.526
Discharge from the hospital	(n = 294)	(n = 7348)	
Antiplatelet regimens			
None	1 (0.34)	1 (0.01)	0.08
Aspirin or thienopyridine only	30 (10.2)	74 (1.0)	<0.001
Dual regimen	259 (88.1)	7238 (98.5)	<0.001
VKA with or without antiplatelet regimen	184 (62.6)	85 (1.2)	<0.0001
1 month	(n = 282)	(n = 7026)	
Antiplatelet regimens			
None	1 (0.36)	18 (0.26)	0.53
Aspirin or thienopyridine only	36 (12.8)	98 (1.4)	<0.001
Dual regimen	245 (86.9)	6894 (98.1)	<0.001
VKA or other anticoagulant	163 (57.8)	104 (1.5)	<0.001
6 months	(n = 280)	(n = 6799)	
Antiplatelet regimens			
None	7 (2.5)	40 (0.6)	0.002
Aspirin or thienopyridine only	63 (22.5)	307 (4.5)	<0.001
Dual regimen	210 (75.0)	6.448 (94.8)	<0.001
VKA with or other anticoagulant	161 (57.5)	124 (1.8)	<0.001
12 months	(n = 264)	(n = 6748)	
Antiplatelet regimens			
None	17 (6.4)	83 (1.2)	<0.001
Aspirin or thienopyridine only	93 (35.2)	1356 (11.0)	<0.001
Dual regimen	154 (58.3)	5304 (78.6)	<0.001
VKA with or other anticoagulant	151 (57.2)	151 (2.2)	<0.001

Values are numbers (%) of observations; VKA = antivitamin K agent.

Table 4
Cumulative rates of adverse clinical events at 30 days, 6 months, and 1 year of follow-up.

	Study group		*P-value*
	VKA	NON-VKA	
1 month	n = 294	n = 7298	
Death	2 (0.68)	27 (0.37)	0.31
Cardiac	1 (0.34)	23 (0.31)	0.61
Myocardial infarction	2 (0.68)	85 (1.2)	0.78
Q-wave	0	14 (0.2)	1.00
Target lesion revascularization	2 (0.68)	33 (0.45)	0.39
Percutaneous	2 (0.68)	33 (0.45)	
Major adverse cardiovascular events[a]	5 (1.7)	115 (1.6)	0.80
Major bleeding	3 (1.0)	36 (0.5)	0.19
6 months	n = 291	n = 7203	
Death	6 (2.0)	65 (0.9)	0.057
Cardiac	2 (0.7)	41 (0.6)	0.68
Myocardial infarction	4 (1.4)	115 (1.6)	1.00
Q-wave	1 (0.4)	20 (0.28)	
Target lesion revascularization	7 (2.5)	96 (1.34)	0.12
Percutaneous	7 (2.5)	91 (1.27)	
Major adverse cardiovascular events[a]	15 (5.2)	225 (3.1)	0.06
Major bleeding	6 (2.1)	58 (0.8)	0.036
12 months	n = 277	n = 6941	
Death	12 (4.3)	119 (1.7)	0.004
Cardiac	5 (1.8)	68 (0.99)	0.20
Myocardial infarction	4 (1.5)	144 (2.1)	0.66
Q-wave	1 (0.4)	25 (0.4)	1.00
Target lesion revascularization	9 (3.4)	179 (2.6)	0.43
Percutaneous	9 (3.4)	164 (2.4)	0.31
Major adverse cardiovascular events[a]	23 (8.3)	367 (5.3)	0.04
Major bleeding	8 (3.0)	83 (1.2)	0.002

Values are numbers (%) of observations.
[a] Patients who experienced >1 MACE are counted only once.

Table 5
Cumulative rates of stent thromboses at 30 days, 6 months, and 1 year of follow-up.

	Study group		*P*
	VKA	NON-VKA	
0–24-h (acute)	n = 296	n = 7343	
Stent thrombosis			
Definite	0	3 (0.04)	1.000
Probable	0	3 (0.04)	1.000
Possible	0	0	–
>24 h–30 days (subacute)	n = 292	n = 7275	
Stent thrombosis			
Definite	0	30 (0.41)	0.6296
Probable	0	17 (0.23)	1.000
Possible	0	0	–
>30 days–12 months (late)	n = 266	n = 6835	
Stent thrombosis			
Definite	1 (0.38)	21 (0.31)	1.000
Probable	0	8 (0.12)	1.000
Possible	2 (0.75)	25 (0.37)	1.000

Values are numbers (%) of observations.

et al. in a matched comparison between BMS and DES did not specify which kind of DES platform was implanted, finding no differences in terms of MACE between the two groups [13]. On the contrary, our analysis represents the largest report on use of a sirolimus-eluting platform in this population. It should be also considered that a bias in the selection process by the operators of patients, who would have benefited from DES, and the withdrawal of VKA regimen in almost half of the patients at 12-month may have influenced the good outcome in the present report as compared to the previous ones.

SES have previously proved to be able to reduce target lesion revascularization in comparison with BMS, not only in favorable lesions and patients [14], but also in more complex lesions, such as total chronic coronary occlusions, vessel restenosis and/or diabetic patients [15–17]. Stenting with SES has been also recently showed as an effective therapeutic option in elderly patients, with acceptable rates of complications and a very low rate of repeat revascularization [18]. Patients under VKA treatment resemble elderly patients, being a population seldom included in clinical trial testing DES, with comorbidity and high risk of bleeding, worsened by a prolonged antiplatelet therapy. Nevertheless, our findings showed that they may safely undergo DES implantation and be treated with dual antiplatelet therapy at the cost of a moderately increased risk of bleeding. It is noteworthy that though a lower usage of dual antiplatelet therapy in VKA than non-VKA patients, the rate of stent thrombosis was very low and comparable between the two groups, further remarking the good safety profile of the SES platform even compared to the 2nd generation DES [19–21]. Conversely, the incidence of bleeding was, as expected, higher in VKA than in NON-VKA group and comparable to previous studies

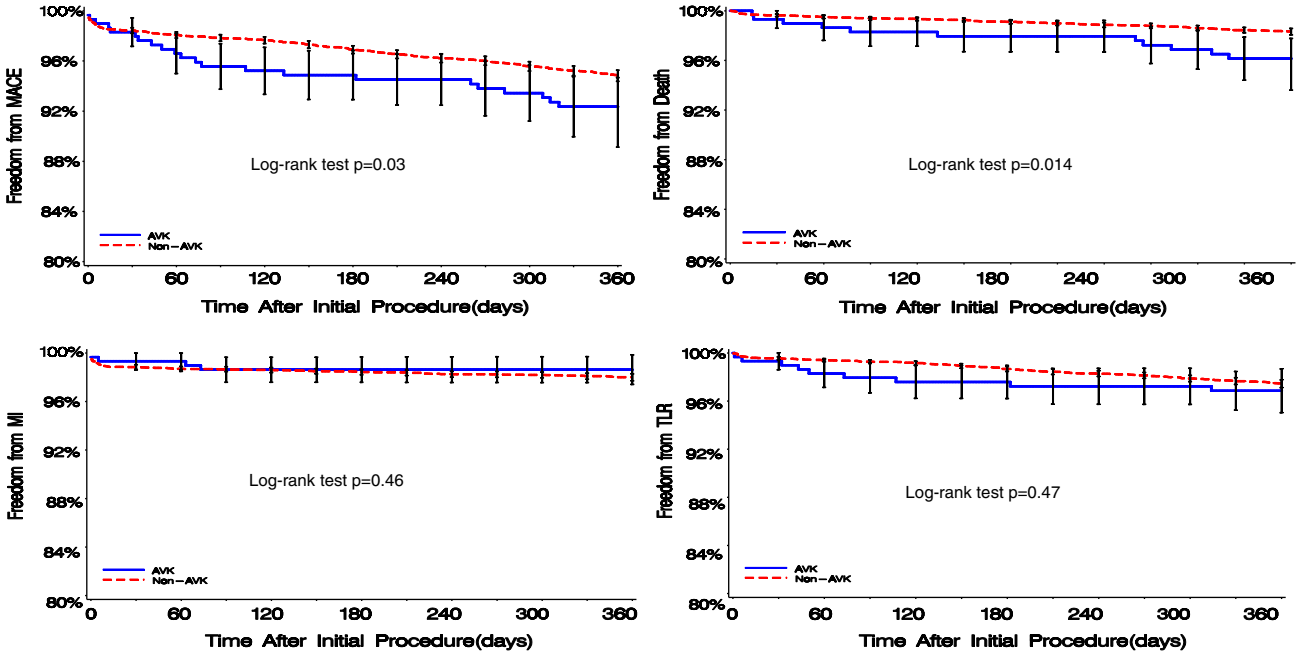

Fig. 1. Kaplan–Meier curves of MACE, all-cause death, myocardial infarction and target lesion revascularization survival between the VKA and NON-VKA groups. MI = myocardial infarction; TLR = target lesion revascularization; VKA = anti-vitamin K treatment.

[7,8,13,22,23]. Future use of new anticoagulant agents could be appealing in order to reduce the major bleeding associated to anti vitamin K agents [24]. Novel trials combining DES and these new agents would be required. Recent consensus did not currently discourage DES use in an VKA population, especially for those patients at low-moderate risk of hemorrhagic events and admitted for acute coronary syndrome, which already implies per se a 12-month duration of antiplatelet therapy independently from the stent implanted [25]. Recently, the Woest study has also shown the safety of using only clopidogrel on the top of VKA agent instead of DAT, without any increase in stent thrombosis and with strong decrease in bleeding event at 1-year follow-up [26].

4.1. Limitations

This analysis is limited by its registry design and by its post-hoc nature. The clinical follow-up, limited to 1 year, precluded the evaluation of very late stent thrombosis and late adverse events. The type of selection process applied in each center is unknown: some of the sicker patients on VKA and those with the highest perceived bleeding risk may have been treated with a BMS and were thus not included. For this reason, the study population is a much selected one and the present findings do not necessarily apply to all patients on VKA who require coronary stenting. Finally, the e-SELECT registry was a real world registry without a predefined antithrombotic regimen in patients on VKA. Therefore, multiple treatment combinations were observed during hospitalization and at discharged from the index procedure. For this reason, it was not possible to define the optimal antithrombotic combination following SES implantation in these high risk patients.

5. Conclusions

Selected patients anticoagulated with VKA agent may safely undergo SES implantation. Those patients may receive a variety of APT regimen at the cost of a moderate increased risk of MB. The optimal regimen, using new anticoagulant drugs in association with APT after SES implantation needs to be determined in future studies.

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Appendix A. Classification of major versus minor bleeding events used for this analysis (Montalescot et al. [6])

*Major bleeding**
- Fatal
- Retroperitoneal, intracranial, or intraocular
- Compromising hemodynamic function and requiring specific treatment
- Requiring a surgical or endoscopic intervention, or the decompression of a closed space to stop or control the event
- Clinically overt, requiring the transfusion of ≥1 unit of packed red cells or whole blood
- Clinically overt, causing a ≥3 g/dl (or ≥10%) decrease in hemoglobin.

Minor bleeding†
- Non-traumatic gross hematuria
- Epistaxis that is prolonged, recurrent, or requiring an intervention
- Gastrointestinal hemorrhage
- Hemoptysis
- Sub conjunctival hemorrhage
- Hematoma > 5 cm in diameter or prompting a new or longer hospitalization
- Clinically overt and causing a 2 to 3 g/dl decrease in hemoglobin
- Requiring the administration of protamine sulfate

* Defined as bleeding that met ≥1criterion.
† Defined as bleeding that met a) no criterion for major bleeding, and b) ≥1 minor bleeding criterion.

Appendix B. Organization of the e-SELECT registry

Steering Committee: Philip Urban, MD (Chair) Geneva, Switzerland; Alexander Abizaid, MD, Sao Paolo, Brazil; Adrian Banning, MD, Oxford, UK; Antonio Bartorelli, MD, Milan, Italy; Vladimir Dzavik, MD, Toronto, Canada; Steven Ellis MD, Cleveland, OH, USA; Runlin Gao, MD, Beijing, China; David Holmes MD, Rochester, MN, USA; Myung Ho Jeong, MD, Gwang Ju, Korea; Victor Legrand, MD, Liege, Belgium; Franz-Josef Neumann, MD, Bad Krozingen, Germany; Christian Spaulding, MD, Paris, France; and Stephen Worthley, MD, Adelaide, Australia.

Clinical event Committee: Emanuele Barbato, MD, Alst, Belgium; Alaide Chieffo, MD, Milano, Italy; Christoph Naber, MD, Essen, Germany; Lisette Okkels Jensen, MD, Odense, Denmark; Koichi Sano MD, Saitama-ken, Japan; and Vankeepvram Srinivas, MD, New York, NY, USA.

Electronic data capture and database management: KIKA Medical, Nancy, France.

Statistical analysis: Cardialysis, Rotterdam, The Netherlands

Study sites monitoring: Covance Clinical Research Organization, Princeton, NJ

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