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One-year clinical outcome of biodegradable polymer sirolimus-eluting stent in patients needing short dual antiplatelet therapy. Insight from the ULISSE registry (ULtimaster Italian multicenter all comerS Stent rEgistry)

Cosmo Godino [a,*], Alessandro Beneduce [a], Giuseppe Ferrante [b], Alfonso Ielasi [c], Carlo Andrea Pivato [a], Mauro Chiarito [b], Alberto Cappelletti [a], Giulia Perfetti [a], Valeria Magni [a], Eugenio Prati [i], Stefania Falcone [d], Adele Pierri [e], Stefano De Martini [f], Matteo Montorfano [a], Rosario Parisi [g], David Rutigliano [h], Nicola Locuratolo [h], Angelo Anzuini [d], Maurizio Tespili [c], Alberto Margonato [a], Alberto Benassi [i], Carlo Briguori [e], Franco Fabbiocchi [f], Bernhard Reimers [b], Antonio Bartorelli [f], Antonio Colombo [a]

[a] Ospedale San Raffaele, Milano, Italy
[b] Ospedale Humanitas, Rozzano, Italy
[c] Ospedale Bolognini, Seriate, Italy
[d] Ospedale Humanitas Mater Domini, Castellanza, Italy
[e] Clinica Mediterranea, Napoli, Italy
[f] Centro Cardiologico Monzino, Milano, Italy
[g] Ospedali Riuniti Marche Nord, Pesaro, Italy
[h] Ospedale San Paolo, Bari, Italy
[i] Hesperia Hospital, Modena, Italy

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ABSTRACT

Background: This study aimed to evaluate real-world clinical outcome of patients needing short dual antiplatelet therapy (S-DAPT) following PCI with Ultimaster® thin-strut, biodegradable polymer sirolimus-eluting stent (BP-SES), which was supposed to induce faster stent endothelialization and reduce device thrombogenicity.
Methods: In this sub-group analysis of patients enrolled in the ULISSE registry, two groups were identified: 1) patients discharged with S-DAPT (≤3-month) due to high bleeding risk or need for urgent major non-cardiac surgery and 2) patients discharged with recommended DAPT (R-DAPT) duration (≥6-month). The primary ischemic-safety and bleeding-safety endpoints were TLF (composite of cardiac-death, target vessel MI, and clinically driven target lesion revascularization), and BARC major bleedings (≥type-3a) at 1-year follow-up. To account for events occurring before DAPT discontinuation we performed 3-month landmark analysis.
Results: 82 patients (5%) were discharged with ≤3-month DAPT (57 ± 27 days), and 1558 patients (94%) were discharged with ≥6-month DAPT (318 ± 75 days). No significant differences between S-DAPT and R-DAPT group were observed in TLF at 1-year (7.9% vs. 4.6%). The rate of BARC major bleeding resulted significantly higher in S-DAPT group (3.9% vs. 0.3%; p = 0.001), with the majority of bleeding events occurring within 3 months. The landmark analysis showed no significant differences in BARC major bleedings between groups (1.4% vs. 0.3%; p = 0.142).
Conclusions: As compared to those treated with R-DAPT (≥6-month), patients needing -S-DAPT (≤3-month) after PCI with Ultimaster® BP-SES had similar rates of 1-year TLF and BARC major bleedings following early DAPT discontinuation.

1. Introduction

The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with stent implantation is still a matter of debate. Balancing between ischemic and haemorrhagic risk represents a critical issue, as well as warranting an optimal stent performance, reducing the risk of restenosis and reintervention [1]. In high bleeding risk patients the clinical need of early DAPT discontinuation should be addressed, according to guidelines, using new-generation drug-eluting stents (DES) followed by shortened DAPT regimen, as the use of bare-metal stents (BMS) can no longer be justified [2–4].

* Corresponding author at: Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy.
E-mail address: cosmogodino@gmail.com (C. Godino).

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The Ultimaster® stent (Terumo, Tokyo, Japan) is a new-generation sirolimus-eluting stent composed of thin strut, cobalt chromium platform, with abluminal gradient coating of sirolimus-releasing biodegradable polymer, which is completely resorbed within 3–4 months, thus reducing local inflammatory response and promoting vessel endothelization. The Ultimaster® biodegradable polymer sirolimus-eluting stent (BP-SES) represents a promising device, balancing safety and efficacy in terms of low rate of target vessel failure (TVF) and target lesion revascularization (TLR) at long-term follow-up, including patients with high-risk clinical profile and complex lesions [5–10]. The DISCOVERY 1TO3 study demonstrated complete very early strut coverage and concomitant minimal neointima hyperplasia within the first month after the Ultimaster® BP-SES implantation, which can potentially favor safer short DAPT duration in high bleeding risk patients [11].

In this context we performed a sub-analysis of the ULISSE registry (ULtimaster Italian multicenter all comerS Stent rEgistry) to assess the real-world clinical outcomes of PCI with Ultimaster® BP-SES in a large unselected cohort of patients discharged with clinical indication to short DAPT duration.

2. Methods

The ULISSE registry is a multicenter independent, single-arm, all-comers, observational registry involving 9 different centers in Italy (Appendix A).

2.1. Study design and patient population

This registry retrospectively holds data on 1660 consecutive patients (2422 lesions) undergoing Ultimaster® BP-SES implantation between July 2014 and August 2016, including both elective and urgent procedures. The selection of the Ultimaster® BP-SES over another DES was performed by the operator without any specific preference and was not based on patient risk or lesion morphology. Patients undergoing primary PCI for acute coronary syndromes (ACS) were also included. The only exclusion criteria was the implantation of a combination of different types of DES or of BMS and DES in the same vessel. Revascularization strategies (e.g., atherectomy, IVUS guidance) as well as stent implantation technique (e.g., direct stenting, bifurcation techniques) were left to the operator's choice. All patients were pretreated with aspirin and a second platelet inhibitor: clopidogrel was preferred over ticlopidine in elective patients, whereas, for urgent procedures, each center was allowed to choose between clopidogrel, prasugrel and ticagrelor, as well as to use glycoprotein IIb/IIIa inhibitors. In all the cases, aspirin was continued indefinitely and a second antiplatelet drug (clopidogrel, prasugrel or ticagrelor) was prescribed according to the patients' risk profile and physician's preferences. All patients enrolled, were prospectively followed to evaluate the efficacy and the safety of the Ultimaster® BP-SES. The study was approved by the Hospital Ethics Committee and each patient provided written informed consent for the procedure, data collection and subsequent analysis. No external source of funding supported this study.

In the present ULISSE subgroup-analysis, we retrospectively identified all patients presenting at least 1 high bleeding risk features or other causes which justified at discharge indication for ≤3-month DAPT duration, subsequently indicated as "short" DAPT group (S-DAPT). In case of more than one bleeding risk condition present in the same patient, the more severe one was indicated. All the other patients who had no high bleeding risk features or other reason to S-DAPT indication were discharged with an indication to ≥6-month DAPT and named "recommended" DAPT group (R-DAPT).

The high bleeding risk features and number of patients discharged with S-DAPT duration because of each feature are shown in Fig. 1 and were as follows [2]:

- Oral anticoagulation planned to continue after PCI (n = 53);
- Planned urgent major non-cardiac surgery in the next 3 months (n = 8);
- Platelet count <100.000/mm^3 (n = 1);
- Known anaemia (defined as repeatedly documented haemoglobin <10 g/dl) (n = 1);
- History of haemorrhagic stroke or ischemic stroke in the previous 3 months (n = 2);
- History of gastrointestinal bleeding or previous major bleeding episodes requiring hospital admission or transfusion for bleeding in the previous 12 months (n = 4);
- Other causes: haematological disorders or any known coagulopathy-determining bleeding diathesis, severe chronic kidney or liver disease, neoplasm, need for glucocorticoids or NSAID for >30 days after PCI, expected non-adherence to >30 days DAPT (n = 13).

In this registry no patient was discharged with >3- and < 6-month DAPT indication [12,13].

The criteria reported above and the planned DAPT duration at discharge were all prespecified into the ULISSE database with the intention to define patients at high bleeding risk or those who were otherwise considered by the operators to be candidates for implantation of Ultimaster® BP-SES (for the demonstrated rapid strut endothelialization) [11]. The Ultimaster® BP-SES was utilized instead of another DES or BMS, due to the perceived need to restrict the DAPT at 3 months or even less, adjusted per each case as clinically indicated and according to the choice of the operator.

2.2. Study device

The Ultimaster® BP-SES consists of a cobalt chromium platform coated with sirolimus (3.9 μg/mm stent length) in a matrix with bioresorbable poly-(DL-lactide-*co*-caprolactone) polymer (PDLLA/PCL = 90/10), which is completely resorbed within 3–4 months. Stent platform features a thin-strut (80 μm) and an open-cell 2-link design [14]. The presence of abluminal instead of circumferential coating confers the dual advantage of (a) reducing the overall drug load in view of a targeted abluminal drug delivery; and (b) enhancing strut endothelialization by leaving the luminal side of the stent free from drug and polymer. Moreover, the novel gradient coating technology, made by a

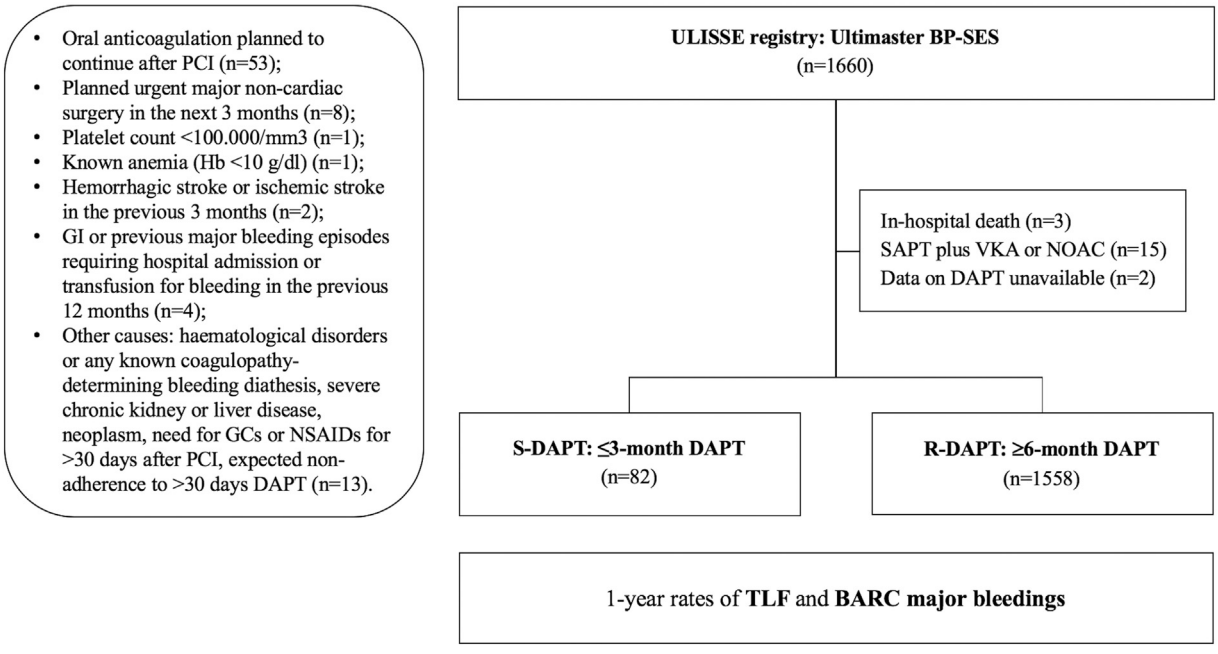

Fig. 1. Study design. In the overall ULISSE registry population, two groups of patients were identified: those presenting at least 1 high bleeding risk feature or other causes (box) which justified an indication for ≤3-month DAPT (S-DAPT), and those discharged with an indication to recommended ≥6-month DAPT (R-DAPT). SAPT = single antiplatelet therapy; VKA = vitamin-K antagonist; NOAC = novel oral anticoagulant; GI = gastrointestinal; GCs = glucocorticoids; NSAIDs = nonsteroidal anti-inflammatory drugs.

slope with the coating multi-layers, and consisting in the absence of drug polymer on the hinges of the stent, reduces the risk of polymer cracking and delamination.

2.3. Definitions, endpoints and data collection

In patients needing short DAPT, in order to evaluate the appropriate balance between preventing ischemic events and causing bleeding, we established as primary *ischemic-safety* endpoint the incidence of target-lesion failure (TLF) at 1-year [composite endpoint of cardiac-death, target-vessel myocardial infarction (TV-MI), and clinically driven target lesion revascularization (TLR)], CENTURY II primary endpoint definition, and as primary *bleeding-safety* endpoint the incidence of major bleedings at 1-year. Major bleedings were defined as bleeding ≥type-3a according to the Bleeding Academic Research Consortium (BARC) classification [5,15]. Additional secondary endpoints were assessed to evaluate safety, including death, all-cause death, MACCE [composite endpoint of all-cause death, MI, target vessel revascularization (TVR) and stroke] and ST (definite, probable, or possible) at 1 year. All clinical outcomes were defined according to the ARC definition [16]. Clinical outcomes and adverse events were prospectively monitored at 3 and 6 months and at 1 year by direct visit, phone interview or contact with referring physician, and specific hospital files were requested when needed. Angiographic follow-up was performed when clinically indicated. In the ULISSE registry, a dedicated database for pre-specified data entry and clinical-event endpoint adjudication has been used, in order to avoid selection bias or incomplete data reports. For data entry control, at each center was required to complete at least 95% of clinical forms in order to be included in the final analysis. All components of both primary and secondary endpoints were evaluated and adjudicated independently by at least two physicians (C.G. and A.B.). In case of a suspected event, the medical records and coronary angiographies from the referring institution were systematically reviewed by an independent experienced interventional cardiologist.

2.4. Statistical analysis

For the purpose of the primary endpoint analysis, patients with no events and with no data after discharge were considered as lost to follow-up. Continuous variables were reported as mean ± standard deviation (SD) or median and compared with Student's *t*-test or Mann–Whitney or Wilcoxon tests, on the basis of the normality of the data (which was verified by Kolmogorov–Smirnov goodness-of-fit test). Categorical variables (such as frequencies or percentages) were compared with χ^2 test without Yates correction for continuity or the Fisher exact test as appropriate [17]. All results are reported on an intention-to-treat analysis. Therefore, S-DAPT and R-DAPT groups are presented as the initial treatment assignment at the time of discharge and not as the treatment eventually received. Patients discharged with no DAPT but a combination of clopidogrel and anticoagulant (n = 15) due to very high bleeding risk, as well as those who experienced in-hospital death (n = 3) and those without information regarding DAPT regimen at discharge (n = 2), were excluded from the intention-to-treat analysis (Fig. 1). Event-free survival assessed at 1 year were evaluated according to the unadjusted Kaplan-Meier method and survival among groups were compared using the log-rank test (Mantel-Cox test). To provide insight into the differences of primary and secondary endpoints rates at 3 months and after 3 months between S-DAPT and R-DAPT groups, a "landmark survival analysis" was performed with a landmark set at 90 days. We excluded patients who died and those lost to follow-up before the landmark time point of DAPT discontinuation. Clinical follow-up was censored at the date of the last follow-up or at 365 days, whichever came first. Data for patients lost at follow-up were censored at the time of the last clinical contact. Two-side p-values<0.05 were considered statistically significant. The statistical analyses were performed using SPSS 24 (SPSS Inc., Chicago, IL, USA). Kaplan–Meier survival curves were generated with GraphPad Prism software (version 6; GraphPad, Inc., San Diego, CA).

Table 1
Baseline clinical characteristics.

	Overall (1660)	S-DAPT (82)	R-DAPT (1558)	p-Value
Clinical characteristics				
Age (years)	68 ± 10	73 ± 7	67 ± 10	<**0.001**
Male gender	1363 (82)	66 (80.5)	1286 (82)	0.680
CKD‡	223 (13.5)	22 (27)	193 (12)	<**0.001**
Hemodyalisis	11 (0.7)	1 (1.2)	9 (0.6)	0.460
Prior MI	413 (25)	23 (28)	386 (25)	0.494
Prior PCI	753 (45)	36 (44)	710 (45)	0.787
Prior CABG	220 (13)	19 (23)	197 (13)	**0.006**
LVEF (%)	53 ± 10	49 ± 12	53 ± 9	<**0.001**
Cardiac risk factors				
DM	485 (29)	25 (30.5)	458 (29.5)	0.818
Hypertension	1225 (74)	63 (77)	1151 (74)	0.522
Dyslipidemia	1032 (62)	49 (60)	977 (63)	0.611
Smoker	473 (28.5)	18 (22)	453 (29)	0.168
Family history of CAD	503 (30)	24 (29)	475 (30)	0.827
Coronary vessel disease				
Single vessel disease	443 (30)	22 (27)	420 (30)	0.849
Two vessel disease	501 (34)	19 (23)	338 (22)	0.861
Three vessel disease	528 (36)	27 (33)	494 (32)	0.961
Clinical presentation				
Stable angina	840 (52)	44 (54)	796 (52)	0.769
ACS	609 (37)	16 (19.5)	572 (37)	**0.002**
Unstable angina	228 (14)	7 (8.5)	219 (14)	0.159
NSTEMI	207 (12.5)	5 (6.1)	197 (12)	0.080
STEMI	174 (10.5)	4 (4.9)	168 (10.5)	0.090
Dual antiplatelet therapy at discharge				
Ticlopidine plus Aspirin	4 (0.2)	1 (0.1)	3 (0.2)	0.185
Clopidogrel plus Aspirin	1224 (74)	78 (95)	1144 (73)	**0.001**
Ticagrelor plus Aspirin	312 (19)	3 (3.6)	309 (20)	**0.001**
Prasugrel plus Aspirin	102 (6)	0 (0)	102 (6.5)	**0.017**
Other therapies at discharge				
Beta blocker*	1223 (74)	61 (74)	1158 (74)	0.430
Calcium channel blocker	391 (23.5)	19 (23)	372 (24)	0.925
Long acting nitrates	199 (12)	14 (17)	185 (12)	0.110
Ivabradine	90 (5)	2 (2.4)	87 (5.5)	0.436
Ranolazine	71 (4)	3 (3.6)	68 (4.3)	1
ACE-I/ARB*	1080 (65)	50 (61)	1024 (65)	0.756
VKA*	94 (6)	41 (50)	42 (2.6)	<**0.001**
NOAC*	20 (1.2)	12 (15)	8 (0.5)	<**0.001**
Statin*	1380 (83)	67 (82)	1306 (83)	0.592

Data are presented as absolute numbers and percentages (for categorical variables) or mean value ± SD (for continuous variables) unless otherwise specified. ‡CKD = Chronic Kidney Disease, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. DM = diabetes mellitus; LVEF = left ventricular ejection fraction; MI = myocardial infarction; CABG = coronary-aortic bypass graft; CAD = coronary artery disease; NSTEMI = non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; ACE-I = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-receptor blocker. *Data updated at May 2018. Bold values indicate significance at p-value <0.05.

3. Results

3.1. Clinical and procedural data

Overall 1660 patients were enrolled in 9 Italian cardiology centers and received at least one Ultimaster® BP-SES. Of these, 82 patients (5%) were discharged with ≤3-month DAPT indication (mean time ± SD 57 ± 27 days; S-DAPT group), and 1558 patients (94%) were discharged with ≥6-month DAPT indication (mean time ± SD 318 ± 75 days; R-DAPT group). Baseline clinical characteristics of study population are illustrated in Table 1. In the S-DAPT group 42 patients (52%) were discharged with an indication for 1-month DAPT and 53 patients (63%) were discharged on triple antithrombotic therapy (40 patients

Table 2
Clinical outcomes at 1-year follow-up.

	Overall (1423)	S-DAPT (76)	R-DAPT (1333)	p-Value
TLF	71 (5)	6 (7.9)	61 (4.6)	0.173
TLR	46 (3.2)	3 (3.9)	42 (3.1)	0.672
TVF	83 (5.8)	7 (9.2)	72 (5.4)	0.151
TVR	62 (4.3)	4 (5.2)	57 (4.3)	0.861
MACCE	105 (7.4)	11 (14)	89 (6.7)	**0.013**
All-cause death	34 (2.4)	6 (7.9)	24 (1.8)	<**0.001**
Cardiac death	25 (1.8)	4 (5.2)	18 (1.4)	**0.008**
Any MI	23 (1.6)	1 (1.3)	21 (1.6)	0.886
TV-MI	19 (1.3)	1 (1.3)	17 (1.3)	1
Stroke	11 (0.8)	2 (2.6)	9 (0.6)	0.050
Major bleeding (BARC≥3)	7 (0.5)	3 (3.9)	4 (0.3)	**0.001**
Definite ST	12 (0.8)	1 (1.3)	10 (0.7)	0.580
Probable ST	4 (0.3)	0 (0)	3 (0.2)	1
Acute ST*	1 (0.1)	0 (0)	1 (0.1)	1
Subacute ST*‡	12 (0.8)	1 (1.3)	9 (0.6)	0.137
Late ST*	3 (0.2)	0 (0)	3 (0.2)	1
Very late ST*	0 (0)	0 (0)	0 (0)	1

1-year clinical outcome was available in 1423 of 1660 eligible patients (86%): in 76/82 (93%) S-DAPT patients and in 1333/1558 (85.5%) R-DAPT patients. TVF = target vessel failure; TVR = target vessel revascularization; MACCE = major adverse cardiac and cerebrovascular event; ST = stent thrombosis. *Definite or probable. ‡In 2 cases subacute ST (definite or probable) occurred in patients not discharged on DAPT. Bold values indicate significance at p-value <0.05.

ASA + clopidogrel + VKA, 1 patient ASA + ticlopidine + VKA and 12 patients ASA + clopidogrel + NOAC: 4 dabigatran, 6 apixaban, 2 rivaroxaban). Compared to R-DAPT patients, those in the S-DAPT group were older, presented a higher rate of chronic kidney disease and previous CABG and lower ejection fraction, were less frequently hospitalized for ACS and more frequently discharged on clopidogrel and anticoagulants, as shown in Table 1.

3.2. Clinical outcomes

Clinical outcomes at 1-year follow-up are reported in Table 2. The primary *ischemic-safety* endpoint TLF (cardiac-death, TV-MI, clinically indicated TLR) occurred in 5% of overall patients and no significant differences were observed between S-DAPT and R-DAPT group (7.9% vs. 4.6%, respectively; $p = 0.173$), as shown in Fig. 2A. Patients in the S-DAPT group presented significantly higher rate of all-cause death (7.9% vs. 1.8%; $p < 0.001$) and cardiac-death (5.2% vs. 1.4%; $p = 0.008$), mainly due to heart failure. Instead, there were no significant differences in terms of any-MI (1.3% vs. 1.6%), TV-MI (1.3% vs. 1.3%) and definite stent thrombosis (1.3% vs. 0.7%, $p = 0.580$). Overall, total definite and probable ST events were 16 and, of these, 1 resulted acute, 12 subacute and 3 late, without significant differences between the two groups, as reported in Table 2. The primary *bleeding-safety* endpoint BARC major bleeding (≥type 3a) occurred in 0.5% of overall patients and resulted significantly higher in S-DAPT group (3.9% vs. 0.3%; $p = 0.001$), as shown in Fig. 2B. In the S-DAPT group, 2 non-fatal intracranial bleedings and 1 gastrointestinal bleeding were reported, all in patients discharged on triple antithrombotic therapy with warfarin. In the R-DAPT group, all major bleedings occurred after the first 3 months. Of these patients, 3 suffered from gastrointestinal bleedings and 1 had post-traumatic subarachnoid hemorrhage.

At the landmark analysis started at 90 days, DAPT discontinuation at 3 months was not associated with higher rates of TLF when compared to DAPT continuation up to 1 year (2.8% vs. 2.7%; $p = 0.965$), as illustrated in Fig. 2A (insert panel). In addition, a similar rate of BARC major bleedings was observed between the two groups (1.4% vs. 0.3%; $p = 0.142$) in the time period between 3-month up to 1-year, as illustrated in Fig. 2B (insert panel).

4. Discussion

The main findings of this multicenter national registry sub-analysis are: 1) patients treated with a short-course ≤3-month DAPT after PCI with Ultimaster® BP-SES because of high bleeding risk or need for urgent major non-cardiac surgery had similar rates of 1-year TLF as compared to those treated with recommended ≥6-month DAPT; 2) the rate of 1-year BARC major bleeding (≥type 3a) was significantly higher in patients treated with a short-course DAPT, due to the higher bleeding risk profile and the wider use of triple antithrombotic therapy in this group; 3) at the landmark analysis started at 3 months, after

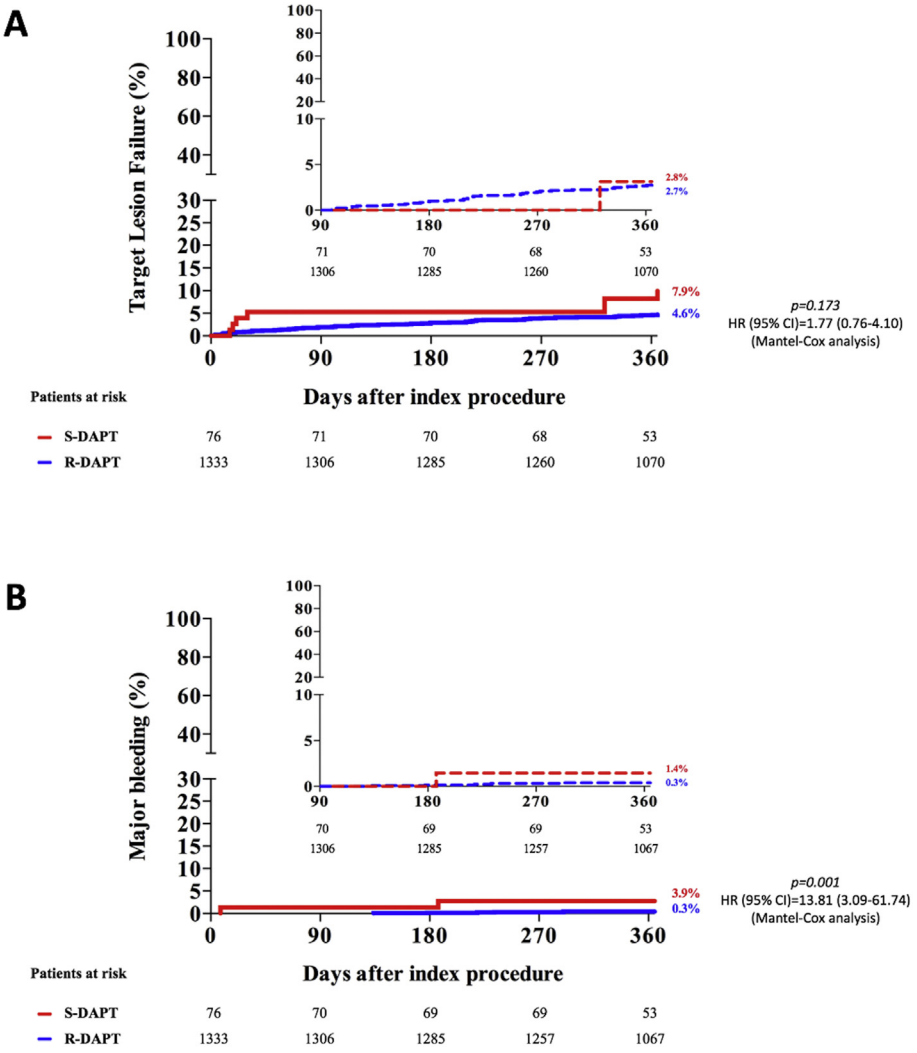

Fig. 2. Kaplan–Meier analysis of TLF (A) and BARC major bleeding (B) events assessed at 1-year follow-up are shown for patients stratified in S-DAPT and R-DAPT. The insert panels respectively show the 3-month landmark survival analysis.

adjustment for adverse events occurring before DAPT discontinuation, BARC major bleeding events resulted similar between the two groups; 4) the incidence of secondary safety endpoints, including MACCE, all-cause death and cardiac death was significantly higher in the group treated with short-course DAPT, reflecting the aforementioned differences in basal clinical characteristics.

Despite the recommendation for DAPT after PCI, premature DAPT disruption due to bleeding or non-compliance is still a relevant issue in clinical practice. Moreover, short-course DAPT is an emerging clinical need, as patients undergoing PCI may require elective surgery or have a high bleeding risk profile [12,13,18]. Several randomized clinical trials and metanalyses explored safety and efficacy of shortened DAPT regimens in PCI with different types of stents, including BMS, first-generation DES and second-generation DES [19–26]. Recently, a subgroup analysis of the I-LOVE-IT 2 trial demonstrated comparable outcomes of 6-month versus 12-month DAPT after implantation of new-generation bioresorbable-polymer DES as compared to a permanent polymer DES (PP-SES) [27]. However, these pivotal studies randomized patients to different DAPT regimens at the time of PCI, including in the outcome analysis adverse events occurring before effective DAPT discontinuation, a potential confounding that could be addressed using a landmark analysis, as previously suggested [20,23]. Furthermore, high bleeding risk patients are poorly represented in these studies and to date few randomized evidences are available to support short-course DAPT regimens in this special population [2–4]. Current European guidelines suggest the possibility of shortened DAPT regimen in patients deemed at high bleeding risk, favoring the use of second-generation DES and new-generation DES over BMS, although the trade-off between bleeding prevention and ischemic risk reduction still remains largely unclear [12,13]. In this context the use of new-generation DES followed by shortened DAPT regimen could represent an interesting option to balance safety and long-term efficacy. Refinements of second-generation DES translated into improved device performance and clinical outcomes, as indicated by the low rate of TLF and TLR, and when compared to first-generation DES or BMS, these devices demonstrated 43% and 62% lower risk of stent thrombosis [28–31]. The implementation of biodegradable polymers technology with new-generation DES, aimed to promote faster and better vessel healing, led the way to a new potential advance, targeting lower in-stent restenosis and [28]. The CENTURY II trial and the recent real-world ULISSE registry have proved the low thrombogenicity of the Ultimaster® BP-SES, with a rate of definite ST comparable to that observed with Xience® permanent polymer everolimus-eluting stent (PP-EES) [5,10]. Promising results, potentially supporting early DAPT discontinuation strategy, came from the DISCOVERY 1TO3 study, as the Ultimaster® BP-SES demonstrated 85.8% and 95.7% strut coverage at 1-month and 3-month after implantation [11]. However, currently, there are still no clinical data regarding the safety of short-course DAPT in high bleeding risk patients after PCI with Ultimaster® BP-SES. In terms of primary *ischemic-safety* endpoint, we observed similar rates of TLF in patients treated with S-DAPT as compared to those treated with R-DAPT (7.9% vs. 4.6%). Interestingly, after adjustment for adverse events occurring before DAPT discontinuation, TLF rate resulted numerically lower in both S-DATP and R-DAPT group (2.8% vs. 2.7%), suggesting that the short-course regimen did not result in higher rate of stent-related ischemic complications. These data compare favourably to those reported in the LEADERS FREE trial, which showed at 1-year follow-up a rate of primary safety endpoint (composite of cardiac-death, MI, or ST) of 9.4% in a selected high bleeding risk population treated with short-course 1-month DAPT after BioFreedom® polymer-free biolimus-eluting stent (PF-BES) implantation [2]. Recently, data from the single-arm LEADERS FREE II study confirmed superior safety and efficacy of the BioFreedom® PF-BES compared to matched BMS controls form the LEADERS FREE trial, showing 8.6% of primary safety composite endpoint (a composite of cardiac death and myocardial infarction) at 1-year in high-bleeding-risk patients treated with 1-month DAPT [32].

In terms of primary *bleeding-safety* endpoint, despite the reduced DAPT duration (mean time 57 ± 27 days), we observed a significantly higher incidence of BARC major bleeding (≥type 3a) in the S-DAPT group (3.9% vs 0.3%; $p = 0.001$), as expected in this high bleeding risk population. Notwithstanding, BARC major bleeding events occurred predominantly in the first 3 months and DAPT discontinuation showed a favorable effect, as the landmark analysis demonstrated similar major bleeding rates between the two groups (1.4% vs. 0.3%; $p = 0.142$) in the time period between 3-month DAPT discontinuation up to 1-year follow-up. These results are in line with those observed in the LEADERS FREE trial, reporting 7.2% rate of BARC major bleeding events in the BioFreedom® PP-BES group [2]. The slightly higher bleeding rate observed in the LEADERS FREE trial can be explained considering the older age (76 ± 9 vs. 73 ± 7 years) and the higher proportion of female (30% vs. 20%) and advanced renal failure patients (18% vs. 10%) as compared to our registry population. Interestingly, in the LEADERS FREE trial 64% of participants were deemed at high-bleeding risk specifically because of age, potentially not representing the clinical practice, while in this sub-analysis of the real-world ULISSE registry, advanced age alone was considered not sufficient to receive S-DAPT and 64% of patients received this therapy in the context of triple antithrombotic treatment [2].

According to the significantly higher clinical risk profile of these patients (older, with higher rate of chronic kidney disease, previous CABG and lower ejection fraction), the rate of all-cause death and cardiac death resulted significantly higher in the S-DAPT group (7.9% and 5.2% respectively), albeit comparable with those reported in the BioFreedom® PF-BES group of the LEADERS FREE trial (8% and 4.2%, respectively) and the LEADERS FREE II study (7.3% and 3.4% respectively) [2,32].

The rate of acute or subacute stent thrombosis in the S-DAPT group resulted low (1.3%) and comparable to that observed in the R-DAPT group, in line with the results obtained with 1-month of DAPT following BioFreedom® PF-BES implantation in the LEADERS FREE trial and in the LEADERS FREE II study (1% and 1.2%, respectively) [2,32]. Moreover, the low rate of TV-MI and definite stent thrombosis in the S-DAPT group was reassuring, not only because these patients were treated with short DAPT, but also because patients at the highest risk for bleeding or affected by major bleeding events are also at the highest risk for stent thrombosis and myocardial infarction.

These favorable results could be related to the specific features of the Ultimaster® BP-SES and hint at the possible safety of this new-generation DES in the context of clinical need for short-course of DAPT. However, considering the non-randomized single-arm design of the present registry, our findings should only be considered hypothesis-generating. Further evaluations are warranted regarding the use of the Ultimaster® BP-SES in comparison with currently available DES with a short-course DAPT in high bleeding risk patients. The ongoing MASTER-DAPT trial (NCT03023020) and the e-ULTIMASTER registry (NCT02188355) will provide new evidence in this growing field.

5. Study limitations

The first limitation of this study is represented by the non-randomized design and retrospective nature, by differences in terms of baseline features among the two groups of patients and by the lack of another DES for a direct comparison. Secondly, as in every real-world registry, clinical follow-up data was not available for 14% of eligible patients and some baseline information were also not attainable. However, none of the patients included in the S-DAPT group was lost to follow-up, thus avoiding the potential bias deriving from its incompleteness. Moreover, a certain level of under-reporting or missing data could exist, even if most of the relevant events were prospectively reported by the investigators in the course of the clinical follow-up or derived from an ad hoc database. Third, this study is not powered enough to discriminate the Ultimaster® BP-SES safety, especially in

terms of stent thrombosis. Fourth, this registry included only Italian centers, thus our results need further confirmation from studies of different world regions. However, we believe that, in view of the ongoing studies in this field, this registry offers important and new information about the clinical outcome of high bleeding risk patients treated with Ultimaster® BP-SES needing short DAPT duration.

6. Conclusions

The results of this registry sub-analysis provide insight into the Ultimaster® BP-SES performance in a large unselected real-world population of patients undergoing short-course DAPT because of high bleeding risk or urgent major non-cardiac surgery. In this setting, patients treated with a short-course ≤3-month DAPT after PCI with Ultimaster® BP-SES had similar rates of 1-year TLF as compared to those treated with a recommended ≥6-month DAPT, with potential reduction of the risk of BARC major bleeding (≥type 3a) events related to DAPT administration. These results can be only considered hypothesis-generating and a large randomized trial will be necessary to prove the theoretical advantage of the BP-SES in patients needing short DAPT duration.

Disclosures

None.

Appendix A

Participating 9 Italian centres-Co-investigators and number of patients treated.

Ospedale San Raffaele, Milano, Italy, 548
Centro Cardiologico Monzino, Milano, Italy, 412
Ospedale Humanitas, Rozzano, Italy, 314
Hesperia Hospital, Modena, Italy, 124
Ospedale Humanitas Mater Domini, Castellanza, Italy, 76
Ospedale Bolognini, Seriate, Italy, 63
Clinica Mediterranea, Napoli, Italy, 49
Ospedali Riuniti Marche Nord, Pesaro, Italy, 38
Ospedale San Paolo, Bari, Italy, 36

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