Cardiovascular Revascularization Medicine 20 (2019) 705–710

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

The Pt-Cr everolimus-eluting stent with bioabsorbable polymer in the treatment of patients with acute coronary syndromes. Results from the SYNERGY ACS registry

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ARTICLE INFO

Article history:
Received 14 August 2018
Received in revised form 8 October 2018
Accepted 15 October 2018

Keywords:
Drug-eluting stent
Bare metal stent
Acute coronary syndrome

ABSTRACT

Objectives: We investigated the safety and efficacy of the bioabsorbable polymer-coated, everolimus-eluting coronary stent (SYNERGY) stent in a real-world study population with acute coronary syndromes (ACS).
Background: A number of clinical trials support the overall efficacy and safety of the SYNERGY stent. However, a recent trial (TIDES-ACS) in the context of ACS reported worrying figures of infarction and definite/probable stent thrombosis in the SYNERGY control arm.
Methods: This is a multicenter registry (10 centers) including consecutive patients with ACS (unstable angina, non-ST elevated myocardial infarction, ST elevated myocardial infarction) who underwent percutaneous revascularization with the implantation of SYNERGY stent. The primary endpoint was the composite of cardiac death, myocardial infarction and target lesion revascularization at 12 months.
Results: A total of 1008 patients were included with age 65.4 ± 14.8 years, 23.8% females and a 24.5% diabetics. Regarding presentation, a 15.2% with unstable angina, 43% with non-ST elevated myocardial infarction and 41.8% with ST elevated myocardial infarction. Primary outcome was met in 3% (7% in SYNERGY TIDES-ACS arm, P superiority <0.01 and 6.3% in OPTIMAX TIDES-ACS arm, P superiority <0.01). Cardiac death was 1.3% (1.6%, p = 0.8 and 0.5%, P superiority =0.1 respectively). Myocardial infarction was 1.6% (4.6%, p < 0.01 and 1.8%, P superiority = 0.9 respectively). Target lesion revascularization was 1% (3.4%, p < 0.01 and 5.4%, P superiority <0.01 respectively). Definite or probable thrombosis was 0.9% (2.8%, p ≤ 0.01 and 1.1%, P superiority = 0.8 respectively).
Conclusions: The results of this registry show a very good safety and efficacy profile at 12 months for the SYNERGY stent in patients with ACS.
Summary: A recent trial (TIDES-ACS) in the context of acute coronary syndromes (ACS) reported worrying figures of infarction and definite/probable stent thrombosis in the SYNERGY stent control arm. We investigated the safety of SYNERGY stent in a real-world study population with ACS applying the same inclusion/exclusion criteria as used in the TIDES-ACS trial. Primary endpoint was the composite of cardiac death, myocardial infarction and TLR at 12 months. A total of 1008 patients have been included. Primary outcome was met in 3% (7% in SYNERGY TIDES-ACS arm, P superiority <0.01 and 6.3% in OPTIMAX TIDES-ACS arm, P superiority <0.01).

Abbreviations: ACS, acute coronary syndrome; BAS, bioactive stents; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; NSTEMI, non-ST elevated myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevated myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularization.

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https://doi.org/10.1016/j.carrev.2018.10.019
1553-8389/

1. Introduction

Evolving changes in drug-eluting stent technology are driven by scientific evidence, gathered on experimental and clinical trials, with the ultimate aim of improving clinical outcomes of patients in all possible clinical settings. The SYNERGY stent (Boston Scientific, Natick, MA, USA) is a new generation of thin strut everolimus-eluting stent with abluminal bioabsorbable polymer which demonstrated to improve vascular healing after implantation and excellent patient outcomes in randomized trials and registries [1–7].

Currently, the most common indication for percutaneous coronary revascularization is the acute coronary syndrome (ACS) [8]. Despite previous studies supporting the safety and efficacy of the SYNERGY stent included also patients with ACS, worrying figures of hard clinical events and stent failure were recently reported as part of the TIDES-ACS trial [9,10]. In that trial, performed in an ACS-only study population, the clinical performance of the OPTIMAX stent, a titanium-nitride-oxide-coated bioactive stents (Hexacath, Paris, France), was compared with the SYNERGY stent. While the rates of the composite primary endpoint of major adverse cardiac events at 12 months were similar for both stent arms, significantly higher rates of cardiac death, myocardial infarction and definite or probable thrombosis were found in the SYNERGY arm of the trial.

Given the reported worrying figures of hard events in the SYNERGY control arm of this trial, and the paucity of data on the use of the SYNERGY stent in ACS-only populations, we investigated the safety of SYNERGY stent in a real-world study of patients presenting with ACS, using the reported results of the TIDES trial as a recent reference.

2. Methods

2.1. Population

This is a multicenter retrospective registry conducted in 10 centers, in which consecutive patients with ACS treated with SYNERGY stents, and with at least one year follow up were included. The same inclusion and exclusion criteria as used in the TIDES-ACS trial were applied for patient selection [9]. Given the retrospective nature of the recruitment, the inclusion and exclusion criteria should be met at the time of the index procedure.

Inclusion criteria: patients with ACS (unstable angina, non-ST elevated myocardial infarction, ST-elevated myocardial infarction) who underwent PCI with the implantation of SYNERGY stent.

Exclusion criteria: age < 18 years; expected survival <1 year; allergy to aspirin, clopidogrel, prasugrel or ticagrelor; allergy to heparins, glycoprotein IIb/IIIa inhibitors or bivalirudin; allergy to everolimus; active bleeding or significant increased risk of bleeding; stent length longer than 28 mm; stent diameter > 4.0 mm; previous coronary artery bypass surgery; aorto-ostial lesion; previous coronary stenting of the target vessel; thrombolysis therapy; cardiogenic shock; planned surgery within 12 months of PCI unless the dual antiplatelet therapy could be maintained throughout the peri-surgical period. At the time of the index procedure a written informed consent for PCI and for use of properly anonymized clinical data was obtained. So, the use of specific informed consent was waived given the retrospective study design provided the complete anonymization of data.

2.2. Study device

The SYNERGY stent is a platinum–chromium balloon expandable stent, with a strut thickness of 74–81 μm covered in abluminal surface with an ultrathin (4 μm) bioabsorbable abluminal lactic acid polymer (PLGA) which elutes everolimus. The drug elution is complete by 90 days, and polymer absorption is essentially complete by 120 days [11].

2.3. Definitions and endpoints

Death was regarded as cardiac in origin unless an obvious non-cardiac cause could be identified. Myocardial infarction was defined according to the third Universal Definition by the European Society of Cardiology and the American College of Cardiology Foundation. Target lesion revascularization (TLR) was defined as either repeat percutaneous or surgical revascularization for a lesion anywhere within the stent or the 5-mm borders proximal or distal to the stent. Stent thrombosis was defined according to the Academic Research Consortium criteria.

The primary endpoint was a composite event rate at 12 months of cardiac death, myocardial infarction and TLR. Secondary endpoints included all cause death, cardiac death, myocardial infarction, any revascularization, TLR, definite or probable stent thrombosis and fatal bleeding at 12 months.

The data was obtained from Hospital records and databases and after adequate anonymization was uploaded into a specifically designed database with standardized criteria for clinical, angiographic and procedural variables. Major adverse cardiac events were adjudicated after review of all submitted clinical data by 3 clinical-interventional cardiologists not involved in the study in order to ensure a uniform and an independent process. The study was approved by the Institutional Review Board. The study was promoted by EPIC Foundation (Fundacion para la Educacion y Promoción de la Investigación en Cardiologia Intervencionista).

2.4. Statistics

Based on the results of TIDES-ACS trial, showing an incidence of the primary outcome at 12 months of 6.3% in the OPTIMAX arm (n = 989) and 7% in the SYNERGY arm (n = 502), the sample calculation for non-inferiority with the OPTIMAX arm accepting a margin of 2.5%, a one-sided type I error rate of 0.025 and a power of 80% yielded as necessary at least 911 patients treated with SYNERGY stent [9,10]. Therefore, the sample size for this registry was estimated in at least 1000 patients. Continuous variables are presented as mean ± standard deviation if following a normal distribution and median and interquartile range if not normal distribution (distribution type was assessed for each variable with the Kolmogorov-Smirnov test). Categorical variables are expressed as percentages. Continuous variables were compared with the Student *t*-test if the data followed a normal distribution and with non-parametric tests if the data were skewed. Categorical variables were compared with the χ^2 squared test or the Fischer exact test, where indicated. Kaplan-Meier curve of event-free survival was obtained. Because no patient-level data was available from the TIDES-ACS trial, no comparative analysis with log-rank test could be performed, then a standard testing pairs of outcomes (χ^2 squared test) was conducted to compare event rates. Values of $p < 0.05$ were considered statistically significant. The statistical packages SPSS 19.0 and Medcalc 12.0 were used throughout.

3. Results

A total of 1008 patients were included in the registry in 10 centers from April 2013 to December 2016. The clinical, angiographic and procedural characteristics of patients are described in Tables 1–2. These characteristics corresponded to a real practice ACS population showing a significantly higher risk profile compared with both arms in TIDES-ACS trial (Table 3). Namely, patients in this registry were older, with more diabetes and more frequent previous cardiovascular events. Regarding angiographic features, patients had more lesions treated along with a worse lesion profile. Furthermore, SYNERGY stents implanted were significantly longer and with smaller diameter. Of note, a longer DAPT period was noted in this registry.

Only 0.9% of patients were lost at follow up. Survival curve for the primary outcome is shown in Fig. 1. The primary outcome was met in a 3% of patients in this registry which was lower than the reported in the SYNERGY TIDES-ACS arm, 7% ($p < 0.01$) and in the OPTIMAX TIDES-ACS arm, 6.3% ($p < 0.01$).

Clinical outcomes are presented in Table 4 and these are shown along with those reported in TIDES-ACS trial in Table 5. Because no patient-level data was available from that trial no comparative analysis

Table 1
Clinical characteristics.

	SYNERGY ACS
	N = 1008
Age, years	65.4 ± 14.8
Females	240 (23.8%)
Diabetes	247 (24.5%)
Insulin treated diabetes	52 (5.1%)
Hyperlipidemia	542 (53.7%)
Hypertension	653 (64.7%)
Current smoker	363 (36%)
Prior MI	120 (11.9%)
Prior PCI	165 (16.4%)
Peripheral vascular disease	93 (9.2%)
GFR, ml/min/1.73 m^2	75.4 ± 24.9
GFR < 60 ml/min/1.73 m^2	201 (20%)
NSTEMI	434 (43%)
STEMI	421 (41.8%)
Unstable angina	153 (15.2%)
Left ventricular ejection fraction, %	54.9 ± 10.3
IIb–IIIa inhibitors	105 (10.4%)
DAPT period, months	11.7 ± 3
DAPT with Clopidogrel	489 (48.5%)
DAPT with Prasugrel	171 (17%)
DAPT with Prasugrel or Ticagrelor	348 (34.5%)
Oral anticoagulation	73 (7.2%)

DAPT = dual antiplatelet therapy; GFR = glomerular filtration rate; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

Table 3
Comparative characteristics with treatment groups of TIDES ACS trial.

	TIDES ACS			
	OPTIMAX	SYNERGY	SYNERGY ACS	
	n = 989	n = 502	n = 1008	p*
Age, years	62.7 ± 11	62.6 ± 10.5	65.4 ± 14.8	<0.001
Females	24.7%	23.7%	23.8%	0.90
Diabetes	14.2%	12.5%	24.5%	<0.001
Insulin treated	2.3%	3.8%	5.1%	0.28
Hyperlipidemia	41.5%	40.2%	53.7%	<0.001
Hypertension	46.8%	43.6%	64.7%	<0.001
Current smoker	31.2%	35.9%	36%	0.95
Prior MI	7.6%	9%	11.9%	0.10
Prior PCI	7%	6.6%	16.4%	<0.001
NSTEMI	46.3%	45%	43%	0.49
STEMI	44.9%	47.6%	41.8%	0.037
Unstable angina	8.9%	7.4%	15.2%	<0.001
N lesions treated	1.17 ± 0.44	1.18 ± 0.49	1.37 ± 0.69	<0.001
Stents/culprit lesion	1.13 ± 0.38	1.14 ± 0.37	1.2 ± 0.47	0.0003
2–3 vessels treated	36%	36.7%	38.8%	0.46
Stent diameter, mm	3.22 ± 1.14	3.19 ± 0.43	3.05 ± 0.48	<0.001
Stent length, mm	18.6 ± 4.7	19 ± 4.9	20 ± 5.2	0.003
LAD treated	45.7%	45.8%	53.5%	0.006
B2/C type lesion	22.5%	21.7%	28.5%	0.005
DAPT, months	10.8 ± 2.7	11.1 ± 2.3	11.7 ± 3	0.001

DAPT = dual antiplatelet therapy; LAD = left anterior descending artery, MI = myocardial infarction; NSTEMI = non-ST elevated myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevated myocardial infarction.
* p values for the comparison SYNERGY ACS vs. SYNERGY TIDES-ACS.

with log-rank test could be performed. So, a standard testing pairs of outcomes was conducted. The use of SYNERGY stent in this registry compared with the OPTIMAX arm in TIDES-ACS trial was associated with a lower incidence of the primary outcome due to less TLR and with comparable incidences for cardiac death, myocardial infarction and definite or probable stent thrombosis.

Among the 29 cases undergoing any kind or revascularization in 12 months follow up, 10 had TLR and 11 had lesions treated that were already present at the time of the index procedure in ACS. The primary endpoint rates for different subgroups are shown in Fig. 2. A significantly higher rate was observed in patients over 75 years old, patients undergoing multivessel PCI and those patients with DAPT interrupted or discontinued within 12 months after the procedure. Regarding the latter group, bleeding events, unexpected urgent surgical procedures and lack of patient adherence accounted for half of cases (n = 44) with the rest having a short DAPT period prescription after index procedure due to a high bleeding risk (n = 45).

Table 2
Angiographic and procedural characteristics.

	SYNERGY ACS
	N = 1008 patients
Radial access	796 (78.9%)
Number of diseased vessels	1.49 ± 0.7
2–3 vessels treated	391 (38.8%)
Lesions treated/patient	1.37 ± 0.69
Stents implanted	1449
Stents/patient	1.44 ± 0.83
Stents/culprit lesion	1.2 ± 0.47
Stent diameter, mm	3.05 ± 0.48
Stent length, mm	20 ± 5.2
	N = 1375 lesions
Left anterior descending artery	737 (53.5%)
Right coronary artery	336 (24.4%)
Left circumflex	305 (22.1%)
B2/C type lesion	393 (28.5%)
Severe calcification	115 (8.4%)
Baseline TIMI 0 flow	304 (22%)
Bifurcation	254 (18.4%)
2 stents technique/bifurcation	39/254 (15.3%)
Rotational ablation	41 (3%)
Intravascular imaging	110 (8%)

4. Discussion

The results of this real-life, multicentre registry supports the safety and efficacy of the thin strut, everolimus-eluting stent with abluminal bioresorbable polymer SYNERGY stent in patients with ACS.

First generation DES durable polymers were considered one of the main causes in precipitating stent thrombosis and delayed in-stent restenosis because of the persistent arterial wall inflammation and delayed vascular healing. Although the current durable polymers are less thrombogenic, it remains a doubt at long term. That is why a huge effort to develop bioabsorbable polymer stents was accomplished. Therefore, the design of drug-eluting stents with bioabsorbable polymers emerged as a promising technology. The SYNERGY stent is a new generation of thin strut everolimus-eluting stent with abluminal bioresorbable polymer which has shown good clinical results in several trials and registries [1–7]. In the EVOLVE II randomized trial, the TLF and TLR rates for the SYNERGY stent were 6.7 and 2.6% at 1 year, respectively [2]. In the all-comers BIO-RESORT study the 1-year TLF and TLR rates in the SYNERGY arm were 4.0% and 2.0% respectively [5]. In a large registry of SYNERGY stent implanted in Asian population, despite almost three quarters of them having complex lesions (type B2 or C), the 1-year TLF rate was 5.8% and TLR rate 1.3% [12].

In a registry of 185 high-risk patients with early discontinuation of dual-antiplatelet therapy (78.4% by 3 months) no stent thrombosis were reported and only three patients required target-vessel revascularization by 1 year [13]. In a study from the Swedish SCAAR registry all implanted SYNERGY stents were compared with other new generation drug eluting stents between 2013 and 2015. The cumulative rate of restenosis (1.1% vs. 1.0%, adjusted HR: 1.24 95% CI: 0.88–1.75; P = 0.21) and stent thrombosis (0.4% vs. 0.5%, adjusted HR: 0.97; 95% CI: 0.63–1.50; P = 0.17) up to 1 year was low in both the SYNERGY group and the other new-DES group [6].

In the bare metal stents arena, an interesting development is represented by the titanium-nitride-oxide-coated bioactive stents. In these stents titanium-nitride-oxide is coated on all the surfaces of the stent,

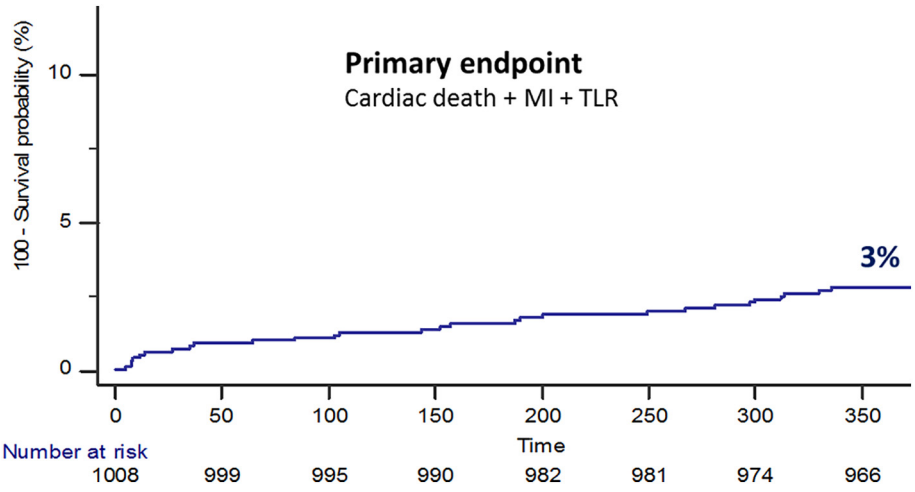

Fig. 1. Survival curve for the primary outcome. The primary outcome (cardiac death, myocardial infarction and TLR at 12 months) was met in a 3% of the cohort.

both inside and outside, through a patented process which results in nitride-oxide particles on the stent surface. Titanium has a better biocompatibility as compared to stainless steel, gold or other surface coating materials, since it offers minimal toxic ion release, a fact that would reduce tissue reaction and inflammation.

In the TITAX-AMI trial, BAS was superior to paclitaxel-eluting stent for the composite endpoint of major adverse cardiac events, cardiac death, reinfarction, and definite stent thrombosis in patients with acute myocardial infarction at 5-year follow-up, with similar rates of ischemia-driven TLR [14,15]. In the BASE-ACS trial, BAS proved non-inferior to durable polymer everolimus-eluting stent for the primary endpoint in patients with ACS at 12-month follow-up; nonfatal myocardial infarction was significantly lower with BAS [16]. In a pooled analysis based on patient-level data from both the TITAX-AMI and the BASE-ACS trials focused in patients with ST-segment elevation myocardial infarction, BAS were associated with lower rates of recurrent myocardial infarction compared to drug-eluting stents at 2-year follow-up; yet, the rates of cardiac death and ischemia-driven target lesion revascularization were similar [17].

Some of the above-discussed trials supporting the safety of the SYNERGY stent included also patients with ACS. However, there is a paucity of data on the clinical outcomes of the SYNERGY stent in ACS-only study populations. Recently the SYNERGY stent and the last generation of the BAS, OPTIMAX stent, have been compared in a trial focused again on patients with ACS, the TIDES-ACS trial [9]. The results of this trial were presented in the 2017 ESC meeting [10]. The primary outcome (composite of cardiac death, infarction and TLR) was met in a 6.3% with OPTIMAX and 7% with SYNERGY stents (p = 0.66). However, cardiac death was higher with SYNERGY (1.6% vs. 0.5%, p = 0.04), myocardial infarction was higher with SYNERGY (4.6 vs. 1.8%, p = 0.004), definite or probable thrombosis was more frequent with SYNERGY (2.8 vs 1.1%, p = 0.01) and finally, TLR was lower with SYNERGY (3.4% vs. 5.4%, p = 0.09). Then, the results of this trial with regards to the SYNERGY stent appeared to be not consistent with results from other trials and registries as previously shown. There are subgroups of patients treated with SYNERGY stents in ACS within larger all-comers trials showing better results, specifically with regards to the thrombosis rates [5]. However, no specific registries for SYNERGY stent in patients with ACS in real practice were available, and this is why this study was designed.

The most important difference between the current registry and the TIDES-ACS trial is the study design, retrospective observational registry vs. randomized controlled trial respectively. Therefore, being aware of the subsequent risk of underreporting of clinical end points in a retrospective observational study like this, a great effort was done to collect properly a complete follow up data for all patients. Nonetheless, another potential reason to explain differences in the results is a difference in the risk profile of the respective study populations. Despite following identical inclusion and exclusion criteria as the TIDES-ACS trial, the patients in our registry showed a significantly higher risk profile, which is likely to be more representative of clinical practice. The difference in risk profile is not surprising, as the process of patient enrollment in randomized clinical trials invariably introduce a far deeper bias that that expected solely by the list of inclusion and exclusion criteria. Of note, despite a higher risk profile, we found a significantly better long-term outcome than patients included in both arms of that trial. The figures for cardiac death, myocardial infarction and stent thrombosis observed in this registry resulted significantly lower than those reported for SYNERGY stent

Table 4
Clinical outcomes at 12 months.

	SYNERGY ACS N = 1008	
Primary endpoint (12 months)		
Cardiac death/MI/TLR	30	(3%)
Secondary endpoints (12 months)		
All cause death	33	(3.3%)
Cardiac death	13	(1.3%)
Myocardial infarction	16	(1.6%)
Any revascularization	29	(2.9%)
Target vessel revascularization	13	(1.3%)
Target lesion revascularization	10	(1%)
Definite or probable stent thrombosis	9	(0.9%)
Definite stent thrombosis	6	(0.6%)
Probable stent thrombosis	3	(0.3%)
Fatal bleeding	1	(0.1%)

MI = myocardial infarction; TLR = target lesion revascularization.

Table 5
Comparative outcomes with TIDES ACS trial at 12 months.

	TIDES-ACS			
	OPTIMAX	SYNERGY	SYNERGY ACS	
	N = 989	N = 502	N = 1008	p*
Primary endpoint				
Cardiac death/MI/TLR	6.3%	7%	3%	<0.01
Secondary endpoints				
Cardiac death	0.5%	1.6%	1.3%	0.10
MI	1.8%	4.6%	1.6%	0.86
TLR	5.4%	3.4%	1%	<0.01
D/P stent thrombosis	1.1%	2.8%	0.9%	0.82

D/P = definite or probable; MI = myocardial infarction; TLR = target lesion revascularization.

* p values for superiority in the comparison SYNERGY ACS vs. OPTIMAX TIDES-ACS. All p values for non-inferiority analysis were significant in the comparison SYNERGY ACS vs. OPTIMAX TIDES-ACS.

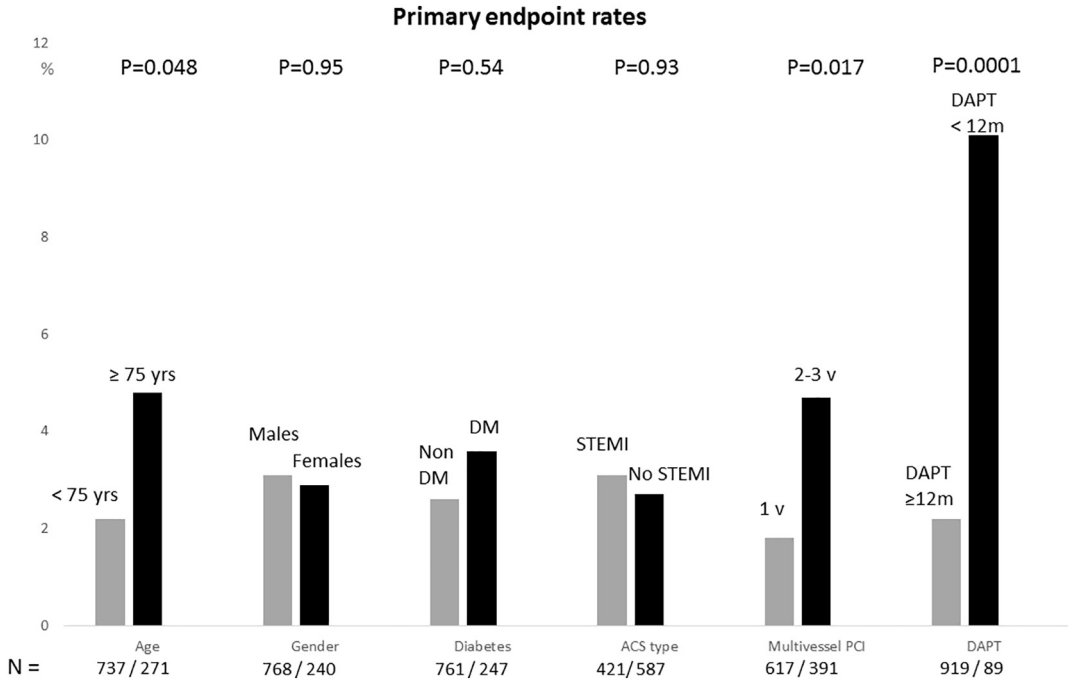

Fig. 2. Primary endpoint rates for different subgroups. The primary endpoint rates were significantly higher in the elderly, in cases undergoing multivessel intervention and those on shorter DAPT.

in the TIDES-ACS trial and appear more consistent with those reported in trials and registries conducted with SYNERGY [1–7,12,13].

5. Limitations

This is a retrospective observational registry and so is affected by the inherent limitations to all observational studies. The use of SYNERGY was left to the operator's discretion. Even though we applied the same inclusion and exclusion criteria and primary outcomes definition, a cross-comparison between studies for the same therapy applied even under comparable conditions is without any doubt of limited value. Nonetheless, the registry shows the results observed with SYNERGY stent in ACS population from real practice and the comparison between this registry and the SYNERGY arm of the TIDES-ACS trial should be interpreted cautiously, only with the intention to put the results of that trial into perspective. The unexpected high rate for thrombosis observed with SYNERGY stent in the TIDES-ACS trial has not been replicated in any of the trials and registries conducted so far with this stent. However, none of those studies was strictly focused on ACS, so that was the rationale for our registry. In this regard, the results in our registry are in agreement with previous ACS subgroups from trials and registries with SYNERGY stent. Retrospective application of enrollment criteria may portend unmeasured sources of bias. Because no patient-level data was available from the TIDES-ACS trial, no comparative analysis with log-rank test could be performed between the three groups. We realize that the standard testing pairs of outcomes used herein is not the most adequate statistical approach. Given the aforementioned limitations the study conclusions do not include any statement about the comparison of SYNERGY stent with the OPTIMAX stent but only the good results observed with the former in this clinical context. Finally, the study was funded by a company with an important conflict of interest in the study, nonetheless the execution and report of the study was totally in charge of the investigators.

6. Conclusions

The results of this multicenter registry show a very good safety and efficacy profile at 12 months for SYNERGY stent in patients with ACS.

Declaration of conflicts of interest

Jose M de la Torre Hernandez: Received unrestricted grants for research from Boston Scientific, Abbott Vascular, St Jude Medical, Biotronik and Biosensors.

Consulting fees from Medtronic and Philips-Volcano Inc.

Nieves Gonzalo: Personal fees from Abbott Vascular for educational events.

Javier Escaned: Personal fees from Boston Sci. and Abbott Vascular for educational events.

Remaining authors: No conflicts to disclose.

This work has not been published previously (except in the form of an abstract) and it is not under consideration for publication elsewhere.

The manuscript has been approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Funding

This is an investigator sponsored study funded by Boston Scientific Group (ISRCAR00143).

Study design, selection of participating centers, collection, management and interpretation of data and manuscript preparation was an exclusive responsibility of the investigators with no involvement/interference of the funding company.

Acknowledgements

Armando Perez de Prado (Hospital de Leon), Jose R Rumoroso (Hospital de Galdacano), Jose F Diaz (Hospital Juan Ramon Jimenez), Eduardo Molina (Hospital Virgen de las Nieves), Ramiro Trillo (Hospital de Santiago de Compostela), Carlos Salazar (Hospital Clinico San Carlos), Santiago Jimenez Valero (Hospital La Paz), Jose R Ruiz Arroyo (Hospital Lozano Blesa), Esteban Lopez Marinaro (Hospital Vall d'Hebron) and Ivan Gomez Blazquez (Hospital 12 de Octubre).

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