SYNERGY—Everolimus-Eluting Stent With a Bioabsorbable Polymer in ST-Elevation Myocardial Infarction: CLEAR SYNERGY OASIS-9 Registry

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Our objective was to evaluate the clinical effectiveness of the SYNERGY stent (Boston Scientific Corporation, Marlborough, Massachusetts) in patients with ST-elevation myocardial infarction (STEMI). The only drug-eluting stent approved for treatment of STEMI by the Food and Drug Administration is the Taxus stent (Boston Scientific) which is no longer commercially available, so further data are needed. The CLEAR (Colchicine and spironolactone in patients with myocardial infarction) SYNERGY stent registry was embedded into a larger randomized trial of patients with STEMI (n = 7,000), comparing colchicine versus placebo and spironolactone versus placebo. The primary outcome for the SYNERGY stent registry is major adverse cardiac events (MACE) as defined by cardiovascular death, recurrent MI, or unplanned ischemia-driven target vessel revascularization within 12 months. We estimated a MACE rate of 6.3% at 12 months after primary percutaneous coronary intervention for STEMI based on the Thrombectomy vs percutaneous coronary intervention alone in STEMI (TOTAL) trial. Success was defined as upper bound of confidence interval (CI) to be less than the performance goal of 9.45%. Overall, 733 patients were enrolled from 8 countries with a mean age 60 years, 19.4% diabetes mellitus, 41.3% anterior MI, and median door-to-balloon time of 72 minutes. The MACE rate was 4.8% (95% CI 3.2 to 6.3%) at 12 months which met the success criteria against performance goal of 9.45%. The rates of cardiovascular death, recurrent MI, or target vessel revascularization were 2.7%, 1.9%, 1.0%, respectively. The rates of acute definite stent thrombosis were 0.3%, subacute 0.4%, late 0.4%, and cumulative stent thrombosis of 1.1% at 12 months. In conclusion, the SYNERGY stent in STEMI performed well and was successful compared with the performance goal based on previous trials. **© 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/)** **(Am J Cardiol 2024;220:111−117)**

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More than a decade ago, first-generation drug-eluting stents (DES) were compared with bare metal stents in patients with ST-elevation myocardial infarction (STEMI) and shown to be superior in The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) trial.[1] This led to the Taxus stent (Boston Scientific Corporation, Marlborough, Massachusetts) being the first DES to be approved by the Food

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See page 117 for Declaration of Competing Interest.

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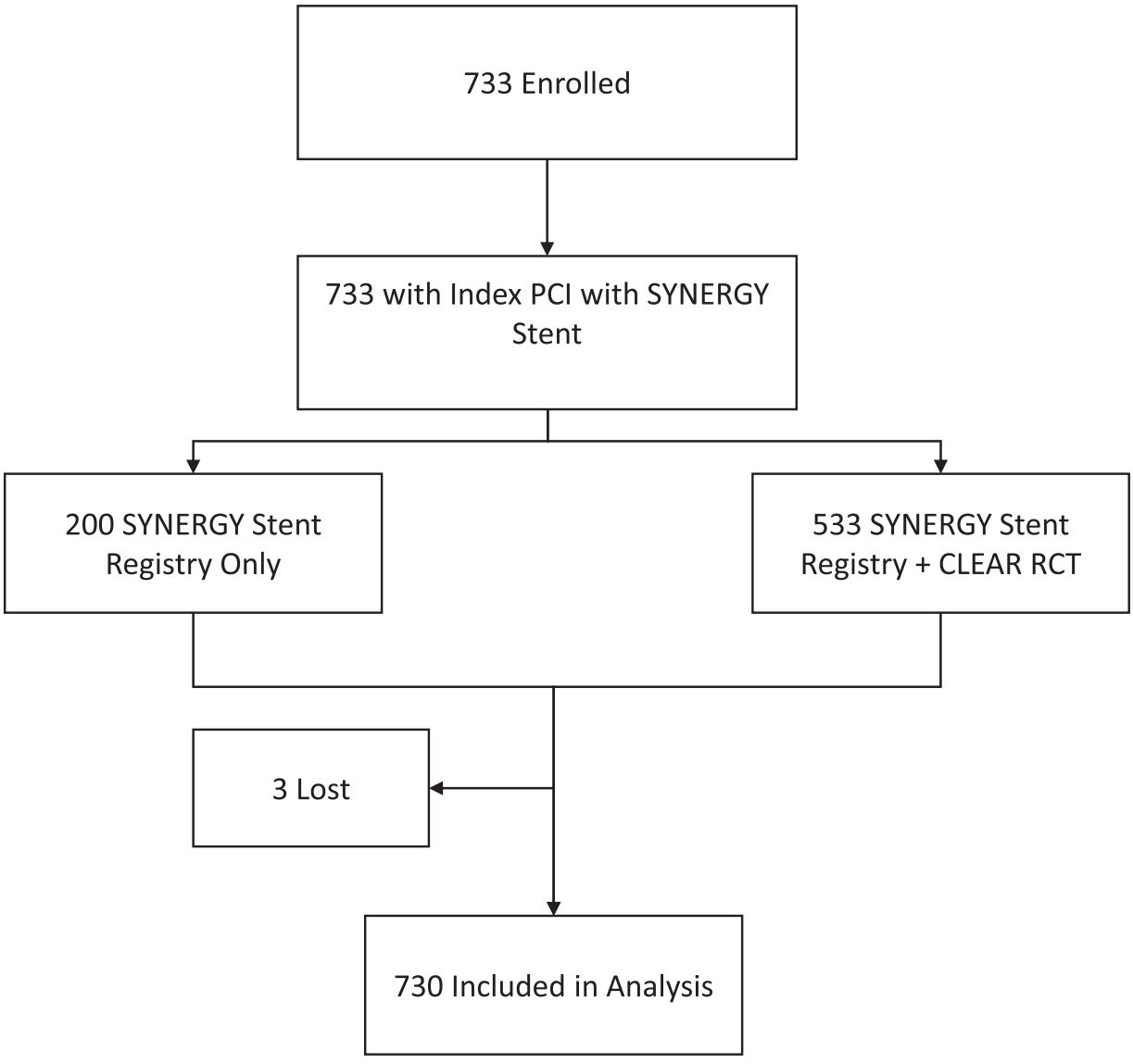


Figure 1. Flow chart.

and Drug Administration for the treatment of STEMI. However, concerns of late stent thrombosis remained with first-generation DES. Data with second-generation DES suggested lower rates of late stent thrombosis.[2]

The SYNERGY stent (Boston Scientific Corporation, Marlborough, Massachusetts) is a newer generation everolimus-eluting stent with a bioabsorbable polymer that has been shown to be non-inferior to permanent polymer everolimus-eluting stent (PROMUS), in the everolimus-eluting stent for the treatment of de-nove Atherosclerotic lesion 2 (EVOLVE) trial.[3]

We undertook a single-arm registry to compare the efficacy and safety of the SYNERGY DES in patients with STEMI compared with a performance standard derived from STEMI patients who underwent percutaneous coronary intervention (PCI) from the Thrombectomy vs PCI alone in STEMI (TOTAL) trial.[4,5]

Methods

The SYNERGY stent registry was a prospective single-arm trial embedded within the CLEAR (Colchicine and spironolactone in patients with myocardial infarction) trial, a 2×2 factorial randomized placebo-controlled trial of colchicine and spironolactone in patients with MI. Patients were able to consent to SYNERGY stent registry alone or both SYNERGY stent registry and randomized drug trial.

Patients with STEMI referred for PCI within 12 hours of symptom onset, with a culprit lesion amenable to stenting, and with planned SYNERGY stent implantation were eligible for the SYNERGY registry. Patients were not eligible if they had a systolic blood pressure <90 mm Hg, known creatinine clearance <30 ml/min/1.73 m^2, or known allergy to everolimus, the SYNERGY stent or any of its components (see online Supplement for detailed inclusion and exclusion criteria). The primary outcome for SYNERGY stent was

Table 1
Baseline characteristics

	Overall-N (%) OR N, median (q1, q3)
Enrolled	733
Age (years) (median q1, q3)	60.0 (53.0, 67.0)
Gender (Female)	176 (24.0)
Weight (kg) (median q1, q3)	83.0 (72.6, 95.0)
BMI (kg/m2) (median q1, q3)	27.7 (24.9, 31.0)
Medical History:	
Previous MI (other than index STEMI)	52 (7.1)
Previous PCI (other than index PCI)	61 (8.3)
Previous CABG surgery	14 (1.9)
Previous Heart Failure	15 (2.0)
Previous Stroke	9 (1.2)
Previous TIA	7 (1.0)
Peripheral Arterial Disease	13 (1.8)
Atrial Fibrillation/Atrial Flutter	18 (2.5)
Hypertension	351 (47.9)
Hyperlipidemia	249 (34.0)
Diabetes	142 (19.4)
Insulin treated	32 (4.4)
Non - insulin treated	109 (14.9)
Smoker	395 (53.9)
Current	300 (40.9)
Former	95 (13.0)
History of Cancer	43 (5.9)
Previous use of oral anticoagulant	14 (1.9)
Systolic blood pressure at presentation (mm Hg)	140.0 (121.0, 158.0)
Heart Rate presentation (bpm)	79.0 (67.0, 90.0)
Location of MI:	
Inferior	384 (52.4)
Anterior	303 (41.3)
Lateral	82 (11.2)
Posterior	48 (6.5)
Heart failure at presentation (Killip class 2 or greater)	57 (7.8)

Table 2
Procedural Variables for primary PCI

	Overall-N (%) OR N, mean (sd), median (q1, q3)
Enrolled	733
Time from symptom onset to hospital arrival - min	168.5 (214.7), 116.0 (60.0, 210.5)
Time from hospital arrival to procedure - min	104.3 (155.4), 72.0 (39.0, 112.0)
Length of Hospital Stay - day	3.4 (3.5), 3.0 (2.0, 4.0)
No of stents	1.3 (0.6), 1.0 (1.0, 2.0)
Stent diameter of SYNERGY Stents	4.0 (1.8), 3.5 (3.0, 4.5)
Stent diameter of non-SYNERGY Stents	3.1 (0.6), 3.0 (2.8, 3.5)
Total stent length	24.3 (7.6), 24.0 (20.0, 28.0)
Radial access	662 (90.3)
Thrombectomy	70 (9.5)
IABP	6 (0.8)
TIMI 0 flow before PCI	494 (67.4)
TIMI 3 Flow pre-PCI	65 (8.9)
TIMI 3 Flow post-PCI	715 (97.5)
Medication use during PCI	
Unfractionated heparin	731 (99.7)
Bivalirudin	2 (0.3)
Enoxaparin	3 (0.4)
Glycoprotein IIb IIIa inhibitor	107 (14.6)
Cangrelor	4 (0.5)
Medication at discharge	
Aspirin	714 (97.4)
Clopidogrel	241 (32.9)
Prasugrel	45 (6.1)
Ticagrelor	437 (59.6)
Beta-blocker	516 (70.4)
ACEI or ARB	546 (74.5)
Statin	689 (94.0)
Anticoagulant	118 (16.1)
Multi-vessel disease	350 (47.7)
RCA	312 (42.6)
Left Main	6 (0.8)
LAD	313 (42.7)
Diagonal	31 (4.2)
Circumflex	121 (16.5)
Graft	2 (0.3)

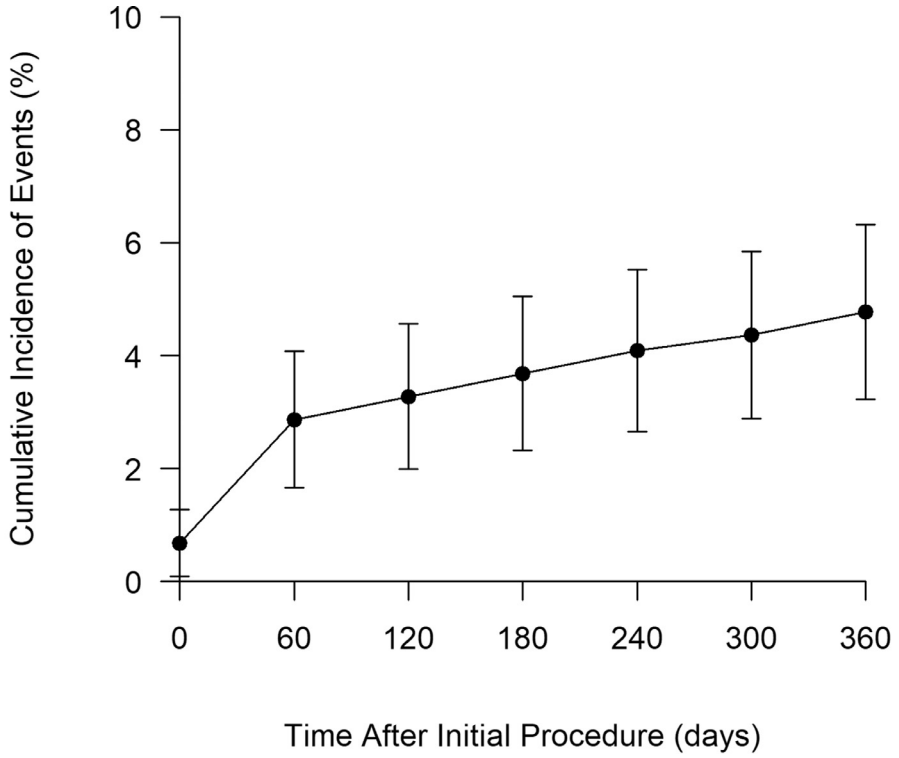
major adverse cardiac events (MACE), defined as the composite of cardiovascular (CV) death, recurrent MI, or unplanned ischemia-driven target vessel revascularization (TVR). The key secondary outcome was definite stent thrombosis within 1 year.

All outcomes were adjudicated by a trained adjudication committee and outcomes of stent thrombosis, target lesion revascularization, and TVR were adjudicated by the angiographic core laboratory at the Hamilton General Hospital.

The SYNERGY stent MACE was evaluated against a performance goal based on data from the recently completed large primary PCI for STEMI trial, TOTAL trial that reported a 1-year MACE rate (CV death, MI, TVR) of 9.3% for the entire population, with 10.2% in bare metal stents and 6.3% for DES.[6] The 1 year MACE (cardiac death, MI, TVR) in HORIZONS AMI trial was 9.5% overall, with 11.1% in Bare metal stents and 8.9% in Taxus DES.[1] In the Everolimus-Eluting Stents Versus Bare-Metal Stents in STEMI (EXAMINATION) trial (n = 1,504), comparing Xience versus bare metal stents in STEMI, the rate of cardiac death, target vessel MI, or target revascularization at 1 year in bare metal stents was 8.4% and 5.9% for the in Xience DES.[7]

Based on the largest trial and published data, we estimated a MACE rate of 6.3% for SYNERGY stent and set a performance goal of 9.45% of CV death, MI, and TVR in 1 year. The performance goal was chosen as it is thought to be clinically appropriate and similar to other pivotal DES trials.

Based on a performance goal of 9.45%, the upper side of the 2-sided 95% CI must be smaller than the performance goal to be successful. Based on these assumptions, using a one-sample z test, 733 patients with SYNERGY DES were needed to be enrolled to have 85% power with a 2% attrition rate. The sample size was calculated a priori. The primary approach was to estimate the incidence of MACE in the 733 STEMI patients with a SYNERGY stent, adjusted for the drug treatments in which they were randomized using a logistic regression model. The SYNERGY stent population was an intent-to-treat population and included all patients who had an attempt at insertion of SYNERGY stent (defined as SYNERGY stent entering guiding



Nnumber at risk	733	712	708	705	700	696	674
Number of events	5	16	3	3	3	2	3

Figure 2. Cumulative incidence of MACE curve.

catheter) irrespective of whether the stent was successfully deployed and irrespective of whether they were randomized in the drug portion of trial.

All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

Results

Between March 29, 2018, and August 10, 2020, 733 patients were enrolled from 30 centers in 8 countries (Figure 1). In this prospective cohort, a history of smoking was common at 53.9%, 19.4% had diabetes mellitus and the median age was 60 years (Table 1). This was a high-risk group with 7.8% presenting with Killip class ≥2 heart failure at presentation. The majority of patients had thrombolysis in MI 0 flow pre-PCI (67.4%), median time from symptoms to hospital arrival was 116 minutes, and hospital arrival to PCI 72 minutes (Table 2). Radial access was the dominant access site with 90.3% and thrombectomy use was uncommon at 9.5%. Unfractionated heparin was the most common anticoagulant given for primary PCI (99.7%).

Median stent diameter of SYNERGY stents was 3.5 mm and length 24 mm with median number of stents 1 (interquartile range 1.2). Ticagrelor was the most common P2Y12 inhibitor (59.6%) followed by clopidogrel (32.9%). Multivessel disease was common with 47.7% and the left anterior descending artery (LAD) (42.7%) was the most frequent culprit artery followed closely by the right coronary artery (RCA) (42.6%). Intravascular imaging during acute STEMI PCI was uncommon in 30 of 733 patients (4%) with intravascular ultrasound (IVUS) in 18 patients and optical coherence tomography (OCT) in 12 patients.

The primary outcome of MACE (CV death, MI, unplanned ischemia-driven TVR) at 12 months was 4.78% (95% CI 3.23 to 6.32%) (Figures 2 and 3, Table 3). The upper bound of 6.32% was below the performance goal of 9.45% meeting the success criteria. The key secondary outcome of definite stent thrombosis at 1 year was 1.1% (8 events) with acute (0 to 24 hours) 0.3%,[2] subacute (24 hours to 30 days) 0.4%[3] and late (30 days to 1 year) 0.4%.[3]

CV death at 1 year was 2.7% (20), recurrent MI was 1.9% (14), unplanned ischemia-driven TVR was 1.0%,[7] and unplanned target lesion revascularization was 0.8%[6] at 1 year.

Subgroup analysis showed that MACE rates were higher in diabetics and the older persons as shown in Figure 4.

Discussion

The SYNERGY stent in patients with STEMI was successful in meeting the performance goal for MACE derived from recent trials. The SYNERGY stent was associated with low rates of stent thrombosis at year (1.1%) and very

Table 3
Primary and other clinical outcomes at 12 months

Outcomes	N(%)	Adjusted Proportion (95%CI)	95% Upper Confidence Bound (%)	Performance Goal (%)
Enrolled	733			
Primary Outcome: MACE	35 (4.8)	4.78 (3.23- 6.32)	6.32	9.45
All Death	24 (3.3)	3.27 (1.99- 4.56)		
Cardiac Death	20 (2.7)	2.73 (1.55- 3.91)		
Non-Cardiac Death	4 (0.5)	0.55 (0.01- 1.08)		
Recurrent MI	14 (1.9)	1.91 (0.92- 2.90)		
Related to TV	8 (1.1)	1.09 (0.34- 1.84)		
Not Related to TV	6 (0.8)	0.82 (0.17- 1.47)		
Unplanned Target Vessel Revascularization	7 (1.0)	0.96 (0.25- 1.66)		
Unplanned Target Lesion Revascularization	6 (0.8)	0.82 (0.17- 1.47)		
Definite Stent Thrombosis	8 (1.1)	1.09 (0.34- 1.84)		
0 to 24 Hours	2 (0.3)	0.27 (0.00- 0.65)		
Definite	2 (0.3)	0.27 (0.00- 0.65)		
Probable	0 (0.0)	NA		
24 Hours to 30 Days	5 (0.7)	0.68 (0.09- 1.28)		
Definite	3 (0.4)	0.41 (0.00- 0.87)		
Probable	2 (0.3)	0.27 (0.00- 0.65)		
30 days to 1 Year	3 (0.4)	0.41 (0.00- 0.87)		
Definite	3 (0.4)	0.41 (0.00- 0.87)		
Probable	0 (0.0)	NA		
Bleeding BARC 2	16 (2.2)	2.18 (1.12- 3.24)		
Bleeding BARC 3 or 5	2 (0.3)	0.27 (0.00- 0.65)		

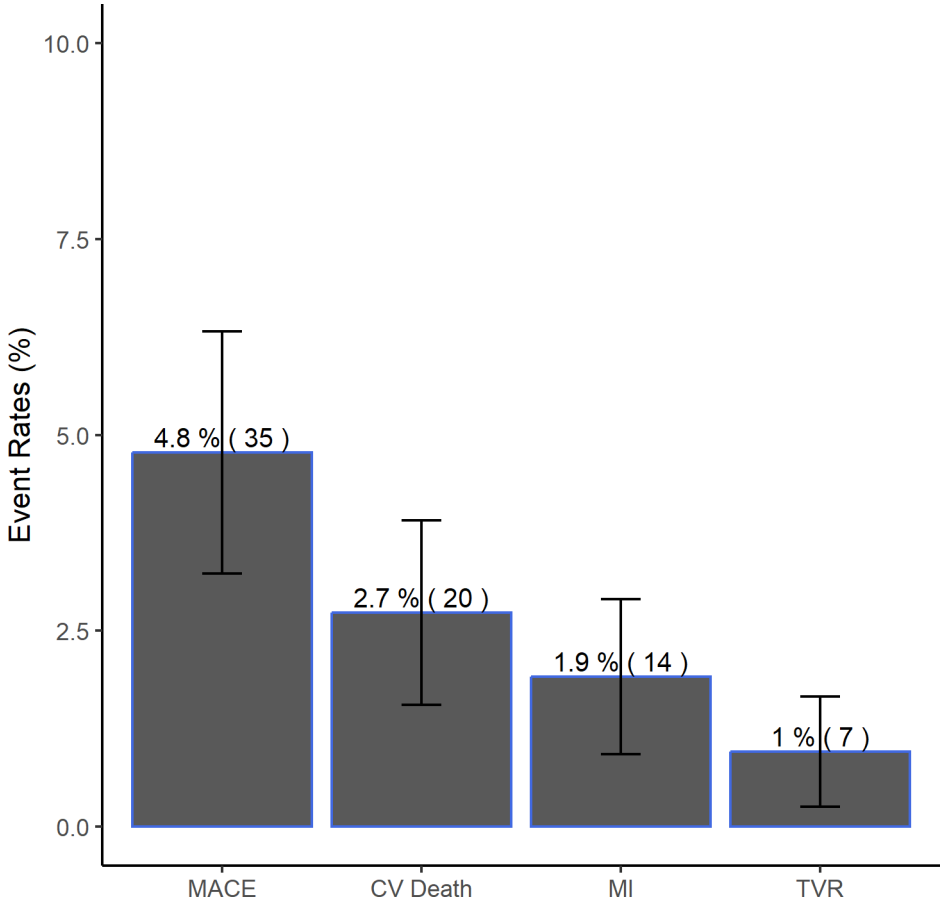


Figure 3. 12 months MACE and components.

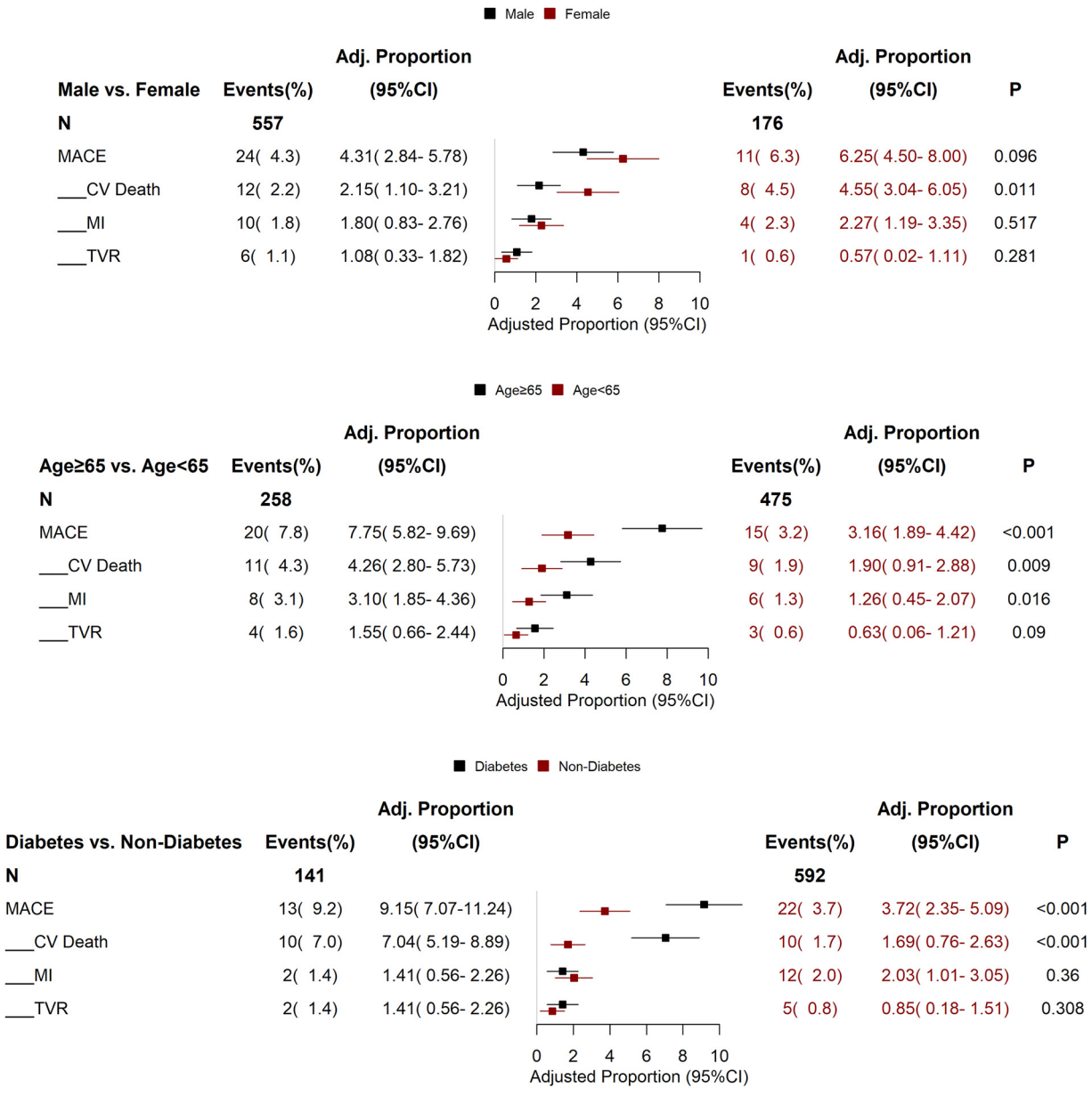


Figure 4. Subgroup analysis for MACE rates.

low rates of acute stent thrombosis within 24 hours (0.3%). These data support that the SYNERGY stent is safe to use during primary PCI for STEMI.

The SYNERGY stent was previously shown to be non-inferior to permanent polymer, everolimus DES in the EVOLVE II (A Prospective Randomized Multicenter Single-blind Non-inferiority Trial to Assess the Safety and Performance of the Evolution Everolimus-Eluting Monorail Coronary Stent System [Evolution Stent System] for the Treatment of a De novo Atherosclerotic Lesions) trial (target lesion failure 6.7% SYNERGY and 6.5% PROMUS Element plus, p = 0.0005 for non-inferiority).[3] The rates of definite stent thrombosis were low (0.2%) and not different. However, patients with STEMI were excluded from the EVOLVE II trial so further data was needed.

The safety and efficacy of DES in patients with STEMI have been a topic of interest for more than a decade. The HORIZONS AMI (The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial randomized 3,006 patients to paclitaxel DES versus bare metal stents showing lower target lesion revascularization and similar rates of MACE with a first-generation DES.[1] Specifically, he rate of CV death, MI, or TVR was 11.% in the bare metal stent group and 8.9% in the paclitaxel stent group, compared with 4.9% in the present study. However, practice has changed and introduced the availability of new P2Y12 agents. More recent STEMI trials that reflect these changes in practice endure, the EXAMINATION (Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction) trial (n = 751) where the Xience DES arm observed a CV death, MI or TVR rate of 5.9%, and the TOTAL trial, where the DES cohort (n = 5,264) observed a rate

of 6.3%. These recent trials were used to derive the performance goal for this trial.

Based on a previous observational study using propensity scoring, there was a concern that acute stent thrombosis may be higher with bioabsorbable polymers than permanent polymer DES (1.2% vs 0.3%; hazard ratio 4.00, 95% CI 1.13 to 14.19).[8] Our study showed a rate of acute stent thrombosis of 0.3% with the SYNERGY stent which is comparable to the permanent polymer DES. These findings support that the rate of acute stent thrombosis with the SYNERGY stent is low.

This study had some limitations. The main limitation is the lack of randomization which allows direct comparison and addresses confounders. The use of a single cohort design with a pre-defined performance goal has been utilized by the Food and Drug Administration with devices with extensive data. Methods to minimize bias included prospective enrollment, the use of trained adjudication committees and angiographic core laboratory for outcomes and broad inclusion criteria including left main and coronary bypass graft lesions which have been previously excluded. Irrespective of these measures, because of the lack of randomization, these results can only be considered hypothesis-generating. Finally, the use of intravascular imaging was low, suggesting that outcomes could be potentially even better with routine intravascular imaging.

In conclusion, in this modern STEMI registry, the SYNERGY stent performed well and was successful compared with the historical performance goal based on previous trials.

Declaration of competing interest

Dr. Jolly reports financial support was provided by Boston Scientific Corp. Dr. Jolly reports financial support was provided by Canadian Institutes of Health Research. Dr. Sabate reports consulting for Abbott Vascular and iVascular. Natalia Pinilla-Echeverri reports consulting for Conavi, Amgen, Bayer, and Novartis; financial support provided by Abbott Vascular; and an advisory board position at Philips. Dr. Mehta reports consulting for and financial support provided by Abbott, Amgen, Bristol-Myers Squibb, HLS Therapeutics, Janssen, Merck, Novartis, and Novo Nordisk. The remaining authors have no competing interests to declare.

CRediT authorship contribution statement

Sanjit S. Jolly: Writing – original draft. **Shun Fu Lee:** Writing – review & editing. **Rajibul Mian:** Writing – review & editing. **Sasko Kedev:** Writing – review & editing. **Shahar Lavi:** Writing – review & editing. **Raul Moreno:** Writing – review & editing. **Gilles Montalescot:** Writing – review & editing. **Ali Hillani:** Writing – review & editing. **Timothy D. Henry:** Writing – review & editing. **Valon Asani:** Writing – review & editing. **Robert F. Storey:** Writing – review & editing. **Johanne Silvain:** Writing – review & editing. **James C.S. Spratt:** Writing – review & editing. **Marc-André d'Entremont:** Writing – review & editing. **Goran Stankovic:** Writing – review & editing. **Biljana Zafirovska:** Writing – review & editing. **Madhu K. Natarajan:** Writing – review & editing. **Manel Sabate:** Writing – review & editing. **Satya Shreenivas:** Writing – review & editing. **Natalia Pinilla-Echeverri:** Writing – review & editing. **Tej Sheth:** Writing – review & editing. **Omar Abdul-Jawad Altisent:** Writing – review & editing. **Núria Ribas:** Writing – review & editing. **Elizabeth Skuriat:** Writing – review & editing. **Jessica Tyrwhitt:** Writing – review & editing. **Shamir R. Mehta:** Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.02.021.

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