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Resolute zotarolimus-eluting stent in ST-elevation myocardial infarction (resolute-STEMI): A prespecified prospective register from the DAPT-STEMI trial

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Abstract

Objectives: To evaluate the safety and efficacy outcomes after primary percutaneous coronary intervention (pPCI) with second-generation Resolute™ zotarolimus-eluting stent (R-ZES) in patients enrolled in the DAPT-STEMI Trial (NCT01459627).

Background: R-ZES is one of the most used drug eluting stents worldwide. To date, the safety and efficacy data of this stent in setting of STEMI is limited.

Methods: The Resolute-STEMI is a prespecified prospective register that reports the safety and efficacy of R-ZES in setting of ST-Elevation Myocardial Infarction (STEMI) at 6 months for the following endpoints: a composite endpoint of all-cause mortality, any myocardial infarction (MI), any (unscheduled) revascularization, stroke and TIMI major bleeding, as well as target lesion failure and stent thrombosis (ST).

Results: From a total of 1,100 STEMI patients enrolled in the trial, 998 received a R-ZES. At 6 months the PE occurred in 42 (4.2%) patients. All-cause death, MI, revascularization, stroke and TIMI major bleeding was respectively 8 (0.8%), 9 (0.8%), 34 (3.4%), 2 (0.2%), and 4 (0.4%). The rate of target lesion revascularizations involving the culprit lesion was 1.1%. Target lesion failure was 1.5%. The rate of definite ST was 0.5%. The rate of both definite or probable ST was 0.7%.

Conclusions: The present analysis is the largest to date reporting short-term and mid-term clinical outcomes with the R-ZES stent in setting of STEMI. At 30 days and 6-months R-ZES has an outstanding safety and efficacy even in this high-risk category of patients.

KEYWORDS
acute myocardial infarction, antiplatelet therapy, coronary artery disease, drug-eluting stent, stent thrombosis

1 | INTRODUCTION

Revascularisation of the acutely occluded vessel by means of primary percutaneous coronary intervention (pPCI) has evolved as the gold standard treatment for patients presenting with ST-elevation myocardial infarction (STEMI). Clinical outcomes, after stenting of the occluded coronary lesion with second-generation rapamycin-like eluting drugs from biocompatible durable-polymers are superior in terms of safety and efficacy as compared to bare metal stents and first generation paclitaxel-eluting stents.[1–3] Zotarolimus-eluting stent has evolved as one of the most used stents worldwide as clinical trials have shown that this device is at least as good as the most studied second-generation DES, the everolimus-eluting stent. Indeed, the Resolute All Comers- as well as the Twente Trial, showed true noninferiority between these two devices.[4,5] Furthermore, sub-analyses of both these trials in STEMI patients, have shown both noninferiority between these devices,[6] however to date, no large-scale prospective data regarding safety and efficacy of Resolute™ Zotarolimus-eluting stent (R-ZES) in setting of pPCI for STEMI patients have been published. Therefore, we present the results of Resolute-STEMI; a prospective international register, a prespecified analysis of the DAPT-STEMI trial,[7] which represents the largest study cohort to date regarding safety and efficacy of R-ZES in setting of STEMI.

2 | MATERIALS AND METHODS

2.1 | Study design

The DAPT-STEMI trial was a prospective, randomized, international open label trial testing the hypothesis that 6 months of dual antiplatelet therapy (DAPT) after second generation R-ZES implantation, in the setting of pPCI for STEMI, is not inferior to 12 months DAPT (noninferiority hypothesis), in terms of a combined endpoint of safety and efficacy. The design of the DAPT-STEMI trial has already been published.[7] Briefly, patients that underwent pPCI with R-ZES in the setting of STEMI were enrolled and if event-free at 6 months were randomized (1:1 fashion) between single antiplatelet therapy (SAPT; aspirin only) versus DAPT for an additional 6 months and followed until 2 years after pPCI as shown in Figure 1. The primary end point (PE) of the trial is a patient oriented composite endpoint of all-cause mortality, any myocardial infarction, any revascularization, stroke and major bleeding (NACCE) at 18-months after randomization. All enrolled patients were followed until 6 months when the randomization took place for event-free patients. All patients gave informed consent for the procedure and approval of the ethics committee was obtained.

The results of the entire study population till 6 months represent a prespecified study: the Resolute-STEMI register (see Figure 1). R-ZES was strongly recommended in the DAPT-STEMI trial however in case of specific size availability other modern generation DES could be used. For the purpose of the RESOLUTE-STEMI, only patient treated with R-ZES, were included. R-ZES is a cobalt-chromium stent with a strut thickness of 89 μm that elutes zotarolimus, a semi-synthetic rapamycin derivative from a three blend composed biocompatible durable polymer coating.

2.2 | Procedures and treatment

STEMI patients between 18 and 85 years who underwent pPCI with a second-generation R-ZES were enrolled. At inclusion, all STEMI patients were treated according to standard clinical practice. Artery puncture site was left to the discretion of the operator, although radial approach was strongly recommended. Thrombosuction and/or predilatation of the lesion was left to the discretion of the operator. DAPT, consisting of aspirin (ASA) 150–300 mg per os or 250–500 mg bolus intravenous (i.v.) followed by 75–100 mg daily, and prasugrel 60 mg loading dose, followed by 10 mg daily, or ticagrelor 180 mg loading dose, followed by 90 mg twice daily were initiated and continued for 6 months. Patients treated with clopidogrel received a 600 mg loading dose followed by 75 mg daily for 6 months. Additional (scheduled) revascularisations in nonculprit lesions, when needed, were performed within 45 days from the pPCI, however, even in this case the 6 month follow-up time point is based on the date of the pPCI.

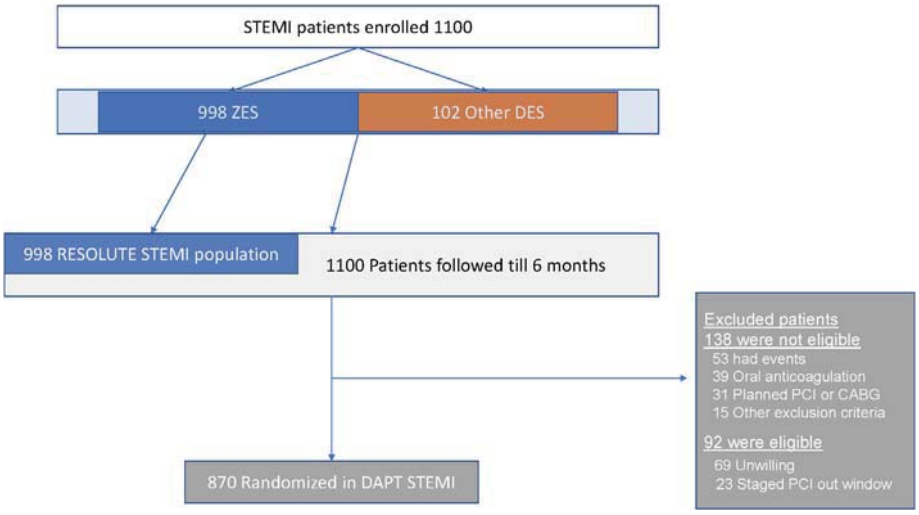

FIGURE 1 Flowchart of RESOLUTE STEMI and DAPT STEMI. CABG, coronary artery bypass graft; DES, drug-eluting stent; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; ZES, zotarolimus-eluting stent [Color figure can be viewed at wileyonlinelibrary.com]

2.3 | Patient follow-up, data collection, and evaluation

Patients were enrolled and follow-up visits took place at discharge, 30 days and 6 months, either by regular clinical visits or telephone. Clinical condition of the patient was evaluated, and adverse clinical events were recorded. Monitoring and event adjudication was performed by an independent clinical event committee (Diagram BV, independent clinical research organization, Zwolle, the Netherlands).

2.4 | Resolute-STEMI endpoints and definitions

The primary outcome of the Resolute-STEMI was a patient oriented composite endpoint of all-cause mortality, any myocardial infarction (MI), any (unscheduled) revascularisation, stroke and Thrombolysis In Myocardial Infarction (TIMI) major bleeding,[8] the net major adverse cardiac and cerebrovascular events (NACE) at 6 months. MI were adjudicated based on the ARC definition.[9] Any revascularization was defined as any clinically indicated revascularisation procedure by PCI or CABG not foreseen at randomization. The major secondary endpoint was the outcome of the primary endpoint at 30 days, other secondary endpoints were the occurrence of definite and probable stent thrombosis (ST) as well as target lesion failure (TLF) at 30 days and 6 months respectively. Definite or probable ST were defined according to the Academic Research Consortium (ARC) criteria.[9] TLF was defined as the composite of cardiac death, target-vessel MI and any target lesion revascularization (TLR). Stroke was defined as an acute neurological event lasting at 24 hr, with focal signs and symptoms, which requires confirmation by computed tomography (CT), magnetic resonance imaging (MRI), or pathological confirmation.

2.5 | Statistical analysis

Baseline characteristics were presented as mean ± standard deviation for continuous parameters and as numbers and percentages for nominal variables. The incidence of the primary and secondary endpoints were calculated by means of Kaplan Maier estimates. Analyses were performed using the SPSS version 25.0 software (SPSS Inc., Chicago, IL).

3 | RESULTS

From a total of 1,100 STEMI patients enrolled in the trial, 998 received a R-ZES. Baseline characteristics of the study population receiving R-ZES are reported in Table 1. Mean age was 60 (*SD* ± 10.6) years, with a predominance of male gender (76%), strikingly half of the population were active smokers. Majority of the patients received clopidogrel (43%), followed by ticagrelor (29%), and prasugrel (28%). In 42% patients the left anterior descending artery (LAD) was the culprit vessel. The number of stents for the culprit lesion per patient was 1.28 ± 0.60 with a length of 26.1 ± 12.8 mm. Nonculprit PCI was performed in 14% of patients. For 72% of the patients the minimum stent diameter was at least 3 mm.

TABLE 1 Baseline characteristics

	N = 998
Patient characteristic	
Age—years	60.0 ± 10.5
Male gender	760/998 (76%)
Body-mass index (kg/m^2)	27.7 ± 4.4
Medical history	
Prior CABG	11/998 (1%)
Prior PCI	51/998 (5%)
Prior myocardial infarction	53/998 (5%)
Stroke or TIA	26/998 (3%)
Peripheral arterial disease	29/998 (3%)
Congestive heart failure	40/998 (4%)
Risk factors	
Diabetes mellitus	133/998 (13%)
Hypertension	447/998 (45%)
Dyslipidaemia	273/998 (27%)
Current cigarette smoker	484/998 (49%)
Family history of CAD	337/998 (34%)
Medication at start of study	
Thienopyridine	
Clopidogrel	434/998 (43%)
Prasugrel	276/998 (28%)
Ticagrelor	285/998 (29%)
Percutaneous coronary intervention	
Infarct related artery	
LM	4/998 (0.4%)
LAD	417/998 (42%)
RCA	398/998 (40%)
LCX	179/998 (18%)
ACC-AHA type B2	357/998 (36%)
ACC-AHA type C	226/998 (23%)
No. of stents total (culprit lesion)	1.28 ± 0.60
Total stent length total−−mm (culprit lesion)	26.1 ± 12.8
Nonculprit PCI	139/998 (14%)
Minimum stent diameter	
<2.5 mm	68/1276[a] (5%)
2.5–3.5 mm	1091/1276 (86%)
>3.5 mm	117/1276 (9%)

[a]The total number of stents used for culprit lesion during index procedure.
CAD, coronary artery disease; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; LAD, left anterior descending; PCI, percutaneous coronary intervention; RCA, right coronary artery; RCX, right circumflex artery; SAPT, single antiplatelet therapy; STEMI, ST-segment elevated myocardial infarction; TIA, transient ischemic attack.

Clinical outcomes at 30 days and 6 months are shown in Table 2. Clinical follow-up was obtained in 98% of patients in the present

TABLE 2 Clinical outcome at 30-days and 6 months

	30 days *N* = 998	6 months *N* = 998
Primary endpoint		
Composite of all-cause mortality, any MI, any revascularization, stroke and TIMI major bleeding (net adverse clinical events)	15 (1.5%)	42 (4.2%)
Secondary endpoints		
Composite of all-cause mortality, any MI, stent thrombosis, stroke and TIMI major bleeding	10 (1.2%)	20 (2.0%)
Death	6 (0.6%)	8 (0.8%)
Cardiac	6 (0.6%)	7 (0.7%)
Stroke	0	1 (0.1%)
Myocardial infarction	4 (0.4%)	9 (0.9%)
Definite stent thrombosis	3 (0.3%)	5 (0.5%)
Probable stent thrombosis	2 (0.2%)	2 (0.2%)
Possible stent thrombosis	0	1 (0.1%)
Target lesion failure[a]	9 (0.9%)	15 (1.5%)
Revascularization	13 (1.3%)	34 (3.4%)
Target vessel (TVR)	7 (0.7%)	16 (1.6%)
Target lesion (TLR)	6 (0.6%)	11 (1.1%)
Target vessel, nontarget lesion (non-TLR TVR)	1 (0.1%)	5 (0.5%)
Nontarget vessel (non-TVR)	6 (0.6%)	18 (1.8%)
Bleeding		
TIMI major	0	4 (0.4%)
BARC type 3	0	4 (0.4%)

Note: Data are presented for the intention-to-treat population. BARC, bleeding academic research consortium; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction.
[a]Target lesion failure is defined as cardiac death, target lesion revascularization, or target lesion myocardial infarction.

registry. The primary endpoint was reached by 42 (4.2%) patients. Eight patients died of which 7 (0.7%) because of a cardiac reason. TLF occurred in 1.5% of the patients. TVR occurred in 16 (1.6%) of the patients, with 11 (1.1%) patients needing TLR and 5 (0.5%) needing non-TLR TVR. The incidence of definite or probable ST at 6 months was 0.7%, of which 0.5% was early and 0.2% was late, respectively, according to the ARC definition.[9]

4 | DISCUSSION

The present study, which represents the largest study cohort dedicated to the evaluation of the safety and efficacy of R-ZES in setting of STEMI, showed a low rate of NACCE in STEMI patients treated with 1 or more R-ZES, with the primary endpoint occurring in 4.2% of patients at 6 months.

Furthermore, the rate of ST (definite or probable) was very low, with an incidence of 0.7% at 6 months, confirming an outstanding device outcome even in this high-risk category of patients.

Only few data regarding clinical outcomes of STEMI patients treated with this second generation stent are available: 122 STEMI patients in the RESOLUTE All Comers[6] and a total of 371 STEMI patients in the RESOLUTE Global Clinical Trial Program (including RESOLUTE International,[10] RESOLUTE China Randomized Controlled Trial,[11] and RESOLUTE China Registry).[12] Therefore the sample size of our analysis, significantly enriches the actual knowledge of outcomes in STEMI patients treated with second generation R-ZES. Indeed, R-ZES is a widely used DES in all-comer patients and this analysis confirmed that it can be used efficiently and safely in STEMI patients as well.

Rates of early definite and probable ST were similar to those found in the RESOLUTE All Comers clinical trial,[6] with 0.8% in that trial versus 0.5% in our trial. The RESOLUTE Global Clinical Trial Program found showed slightly higher rates of early ST of 2.0%,[10–12] in the Twente trial, the incidence of early ST was 0.2% in patients receiving a R-ZES, however STEMI patients were excluded.[4] The low rate of adverse events with this second-generation stent may be the result of improvement of the stent characteristics like thinner stent struts as well as the use of a biocompatible polymer.

Indeed, thinner stent struts favor a better and homogeneous endothelial strut coverage as compared to the thicker stainless steel struts of the first-generation DES,[13] and DES with thin struts have shown a low risk of adverse cardiovascular events in patients with a variety of clinical syndromes.[14] The R-ZES uses a biocompatible durable polymer that enables longer drug elution and has shown to significantly affect the amount of neointima compared with the previous zotarolimus-eluting platform.[15] Moreover, OCT studies have demonstrated essentially complete endothelial coverage at 3 months with this device.[16]

Thus, the low event rates in-patient with myocardial infarction treated with PCI with the second-generation stent as compared to first-generation DES, might be attributed to the improved design of these devices.[17]

Moreover it has been shown that patients who discontinued DAPT between 1 and 12 months after implantation of the R-ZES had low rates of ST and adverse cardiac outcomes[18] and recently the DAPT STEMI trial provided an important answer regarding the noninferiority of 6 months of DAPT compared to 12 months DAPT after R-ZES implantation in the setting of pPCI for STEMI.[19] Indeed 6-month DAPT was noninferior in a patient-oriented composite clinical endpoint versus the regimen of 12 months DAPT showing that a shorter DAPT duration is also feasible and safely applicable if clinically required in STEMI patients who received a R-ZES.

5 | CONCLUSIONS

The present analysis is the largest to date reporting outcomes with the R-ZES stent in STEMI patients. At 30-days and 6-months, the Resolute-STEMI Prospective Registry confirmed that the safety and the efficacy of this device is outstanding even in this high-risk category of patients.

6 | LIMITATIONS

This prespecified sub-analysis had some limitations, that have to be addressed. Firstly, it has the general intrinsic limitations of a prospective registry. Secondly, no standard coronary angiography was performed at follow-up, however, clinically relevant stent related outcomes were addressed in the registry. Finally, per protocol, the choice of the P2Y12 inhibitor prescribed was at the operators' discretion reflecting the ESC guidelines at the time when this trial was designed. However, potential differences in outcomes between patients treated with different P2Y12 inhibitors can only be appreciated in studies with much larger size than our present trial.

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