Non-Inferiority of Resolute Integrity Drug-Eluting Stent to Benchmark Xience Drug-Eluting Stent

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Background: The Resolute Integrity coronary drug-eluting stent (DES), the next evolution of the Resolute DES, is designed with thinner stent struts and continuous sinusoidal technology to further enhance performance. This study evaluated the performance of the Resolute Integrity DES compared with the historical performance of Xience V.

Methods and Results: We assessed the safety, efficacy, and deliverability of Resolute Integrity compared with the Xience DES, the prespecified historical control, in PROPEL, a large, real-world prospective, single-arm, open-label study. A total of 1,204 subjects were enrolled in PROPEL and treated with the Resolute Integrity DES at 76 sites in Japan. Lesion and procedural success rates were 100% and 99%, respectively. Patients were equally complex in the Resolute Integrity and Xience cohorts. At 1 year in the clinical-only cohort, the primary endpoint target lesion failure was 4.3% (34/800) in the Resolute Integrity cohort compared with 8.5% (97/1,142) in the Xience historical controls ($P<0.001$ for non-inferiority). Target vessel failure, major adverse cardiac events, target vessel myocardial infarction, and the composite cardiac death and target vessel myocardial infarction were all lower with Resolute Integrity compared with Xience, including in “high risk” patients.

Conclusions: In the large, prospective, multicenter PROPEL trial, the performance of the Resolute Integrity DES was non-inferior to that of the benchmark Xience DES used as a historical comparator.

Key Words: Drug-eluting stents; PROPEL; Resolute Integrity; Xience

The 1st-generation drug-eluting stents (DES) significantly reduced the risk of in-stent restenosis as compared with bare metal stents, but were associated with an increased risk of late and very late stent thrombosis (ST),^{1,2} likely related to delayed healing, inflammation, and neoatherosclerosis.^{3–9} This issue was addressed by 2nd-generation DES, which used anti-inflammatory polymer coatings to elute an antiproliferative drug.^{10,11} The RESOLUTE All-Comers trial demonstrated similar outcomes with the Resolute™ DES (Medtronic, Santa Rosa, CA, USA) and Xience™ DES (Abbott Vascular, Santa Clara, CA, USA).^{12,13} With the advent of 2nd-generation DES, they have been used in evermore complex procedures, making deliverability and the need to reduce the risk of procedural-related complications

increasingly important. Percutaneous coronary intervention (PCI) is being offered to complex patient populations, such as those with diabetes mellitus, small coronary vessels and diffuse disease, total coronary occlusions, bifurcation lesions, and prior myocardial infarction (MI).^{13–16} We assessed the safety, efficacy, and deliverability of the 3rd-generation Resolute Integrity™ DES (Medtronic) in a large, real-world patient population compared with a pre-specified historical control, the Xience DES, from the RESOLUTE All-Comers trial.

Methods

Device Description

The Resolute Integrity DES is the subsequent iteration

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Clinical Trial Registration: URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01808391.

A complete list of investigators in the PROPEL trial is provided in **Appendix S1**.

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Figure 1. Patient disposition in PROPEL to 12 months. *Angiographic follow-up in RESOLUTE All-Comers occurred at 13 months. At 12 months, all RESOLUTE All-Comers patients had clinical-only follow-up.

Table 1. Baseline Characteristics of Patients Treated With Resolute Integrity in the PROPEL Clinical-Only Cohort vs. Xience Historical Controls

	Resolute Integrity (n=905)	Xience (n=1,152)	P value
Age (years)	69.7±9.6	64.2±10.8	<0.001
Male	702 (77.6)	889 (77.2)	0.874
Diabetes mellitus	377 (41.7)	270 (23.4)	<0.001
Insulin-dependent	69 (7.6)	82 (7.1)	0.671
History of hypertension	734 (81.1)	821 (71.3)	<0.001
History of hyperlipidemia	685 (75.7)	780 (67.7)	<0.001
Current smoker	181 (20.0)	305 (26.5)	<0.001
Prior MI	190/899 (21.1)	341/1,120 (30.4)	<0.001
Prior PCI	359 (39.7)	370 (32.1)	<0.001
Prior CABG surgery	34 (3.8)	110 (9.5)	<0.001
LVEF <30%	16/797 (2.0)	13/608 (2.1)	0.853
Renal insufficiency (creatinine ≥140 μmol/L)	84/905 (9.3)	35/1,126 (3.1)	<0.001
Reason for revascularization			
Silent ischemia	183 (20.2)	0 (0.0)	<0.001
Stable angina	416 (46.0)	416 (36.1)	<0.001
Unstable angina	152 (16.8)	218 (18.9)	0.225
Acute MI (<72 h after onset of symptoms)	97 (10.7)	332 (28.8)	<0.001
ST-segment MI	79/97 (81.4)	186/332 (56.0)	<0.001

Results presented as mean ± SD, n (%), or n/N (%). CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

of the Resolute DES and features continuous sinusoidal technology, in which a single continuous wire composed of a cobalt alloy has a sinusoidal design, wound around a mandrel, and then laser-fused at specific crowns to create its final shape. Resolute Integrity differs from conventional

DES, which are laser-cut tubes, and from the Resolute DES, which is formed by fusing together sinusoidal rings. Continuous sinusoidal technology is hypothesized to improve stent deliverability, reduce abrasion during delivery, and improve stent conformability and apposition to the

Table 2. Baseline Lesions and Successful Procedural Outcomes in PROPEL, Stratified by All Patients and the Angiographic Cohort

Lesion characteristics	All patients (n=1,204 patients, 1,522 lesions)	Angiographic follow-up cohort (n=299 patients, 393 lesions)
Vessel location per lesion		
Left anterior descending artery	651 (42.8)	162 (41.2)
Left circumflex artery	336 (22.1)	93 (23.7)
Right coronary artery	496 (32.6)	128 (32.6)
Left main coronary artery	36 (2.4)	10 (2.5)
Bypass graft	3 (0.2)	0 (0.0)
Severe calcification	165/1,484 (11.1)	33/362 (9.1)
Thrombolysis in Myocardial Infarction flow 0	147/1,494 (9.8)	34/372 (9.1)
Preprocedure reference vessel diameter, mm	2.7±0.5	2.8±0.5
Long lesion (≥20 mm)	381/1,436 (26.5)	118/364 (32.4)
AHA/ACC B2/C lesion	1,193/1,500 (79.5)	213/337 (83.0)
Patient SYNTAX score	11.1±8.0	10.5±7.8
Chronic total occlusion	64 (5.3)	19/373 (5.1)
Success		
Lesion success	1,494/1,494 (100.0)	373/373 (100.0)
Device success	1,464/1,496 (97.9)	369/375 (98.4)
Procedural success	1,171/1,179 (99.3)	281/281 (100.0)

Results presented as mean ± standard deviation or n (%). ACC, American College of Cardiology; AHA, American Heart Association.

Table 3. The 10-Month Angiographic Outcomes in the PROPEL Angiographic Cohort

	Angiographic cohort (n=254 lesions)
Diameter stenosis, %	
In-segment	24.1±13.1
In-stent	15.3±12.4
Late lumen loss, mm	
In-segment	0.16±0.37
In-stent	0.26±0.4
Minimal lumen diameter, mm	
In-segment	2.1±0.5
In-stent	2.5±0.6
Binary restenosis rate, %	
In-segment	4.7 (12)
In-stent	3.5 (9)

Results presented as mean ± SD or % (n).

vessel wall. Similar to the Resolute DES, the Resolute Integrity DES utilizes the biocompatible polymer BioLinx™, which has been shown in preclinical studies to elicit minimal inflammatory response,^{17–19} and therefore retains the same drug elution characteristics.

Study Design

The Prospective Multicenter Post-Approval Study to Evaluate the Long-Term Efficacy and Safety of the Resolute Integrity in Japanese All-Comers Patients With Coronary Artery Disease (PROPEL) is a multicentre, prospective, historical control study in an all-comer population. The primary endpoint is 12-month target lesion failure (TLF) with Resolute Integrity compared with a prespecified historical control, the Xience V DES arm in the RESOLUTE All-Comers trial.^{12,13} Because patients in Japan typically undergo angiographic follow-up before 12

months, an angiographic follow-up cohort was established, with angiographic follow-up scheduled at 10 months post-implantation. However, angiographic follow-up in RESOLUTE All-Comers was not performed until 13 months. Therefore, outcomes after implantation with Resolute Integrity in the PROPEL clinical-only cohort are compared with those from the Xience arm in RESOLUTE All-Comers (Figure 1).

Patient Population

Minimal inclusion and exclusion criteria were applied in PROPEL. Patients were >20 and <85 years old with symptomatic coronary artery disease (i.e., clinical indication for PCI with at least 1 coronary lesion visually confirmed on angiography with >50% diameter stenosis). Vessel diameter was required to be 2.5–3.5 mm. Exclusion criteria included cardiogenic shock, contraindications for aspirin or clopidogrel, pregnancy, and planned or elective surgery within 6 months of PCI. Dual-antiplatelet therapy (DAPT) was recommended for at least 6 months after stent implantation. Clinical follow-up occurred at 30 days and 9 and 12 months in all patients, and angiographic follow-up in the angiographic cohort at 10 months.

Study Funding and Oversight

The PROPEL trial was funded by Medtronic Japan and sponsored by the Associations for Establishment of Evidence in Interventions (Tokyo, Japan), which oversaw the study. The study complied with the Declaration of Helsinki, and was approved by the appropriate institutional review board at each study center. Written informed consent was given by all patients. The study included an executive operation committee, a data monitoring committee, and an independent clinical event committee. The data coordinating center (Soiken, Inc., Tokyo, Japan) provided all of the site monitoring. The angiographic core laboratory (Cardiovascular Imaging Core Laboratory, Tokyo, Japan) measured all angiographic endpoints (at both baseline and at 10 months).

Figure 2. The 12-month incidence of target lesion failure with Resolute Integrity in the PROPEL clinical-only cohort compared with Xience historical control.

Table 4. The 12-Month Incidence of Cardiovascular Events in Patients Treated With Resolute Integrity in the PROPEL Clinical-Only Cohort vs. Xience Historical Control

	Resolute integrity (n=800)	Xience (n=1,142)	P value*
Target lesion failure	34 (4.3)	97 (8.5)	<0.001
Target vessel failure	41 (5.1)	111 (9.7)	<0.001
Major adverse cardiac events	42 (5.3)	112 (9.8)	<0.001
Cardiac death or target vessel myocardial infarction	9 (1.1)	63 (5.5)	<0.001
Death	15 (1.9)	31 (2.7)	0.289
Cardiac death	8 (1.0)	19 (1.7)	0.243
Noncardiac death	7 (0.9)	12 (1.1)	0.817
Target vessel myocardial infarction	1 (0.1)	48 (4.2)	<0.001
Clinically driven target lesion revascularization	26 (3.3)	39 (3.4)	0.898
Clinically driven target vessel revascularization	33 (4.1)	55 (4.8)	0.507
Major bleeding	4 (0.5)	NA	NA
Academic Research Consortium definite/probable stent thrombosis	2 (0.3)	8 (0.7)	0.212
Definite	2 (0.3)	3 (0.3)	1.000
Probable	0 (0.0)	5 (0.4)	0.082

Results presented as n (%). *P value adjusted by a prespecified propensity score model as defined in the Methods section.

Endpoint Definitions

All endpoints were defined identically to those in the RESOLUTE All-Comers trial.^{12,13} TLF was defined as cardiac death, target vessel MI (TV-MI), or clinically driven target lesion revascularization (TLR). Target vessel failure (TVF) was defined as cardiac death, MI, or clinically driven target vessel revascularization by percutaneous or surgical methods. Major adverse cardiac events (MACE) were defined as all-cause death, MI, emergency coronary artery bypass surgery, or repeat clinically indicated TLR by percutaneous or surgical method. ST was defined according to the Academic Research Consortium (ARC) definition.²⁰ Major bleeding was defined by the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial definition.²¹ Patients were categorized as “high risk” if they met at least 1 of the following criteria: diabetes mellitus, previous MI, previous coronary revascularization, renal insufficiency (creatinine level $\geq 140 \mu\text{mol/L}$), left ventricular ejection fraction $\leq 30\%$, and age ≥ 75 years. This definition was based on patient characteristics found to pose high risk for cardiovascular events in past studies of PCI.^{22–25}

Lesion success was defined as attainment of $<50\%$ residual stenosis of the target lesion using any percutaneous method. Device success was defined as lesion success using only the Resolute Integrity stent. Procedural success was defined as lesion success and no in-hospital MACE.

Statistical Analysis

This trial was powered for a prespecified non-inferiority testing of TLF at 12 months comparing Resolute Integrity in the clinical-only cohort to a historical control, the Xience arm in the RESOLUTE All-Comers trial, with a non-inferiority margin of 3.5% after propensity score adjustment. The TLF rate observed in the historical control was 8.5% (97/1,142). Assuming the TLF rate in the Resolute Integrity arm would be the same as in the historical control, with a 1-sided type I error of 0.05, a total of 900 patients in the clinical cohort yielded 84% power to demonstrate non-inferiority, assuming a 10% lost-to-follow-up rate. Given possible differences in the baseline characteristics of patients treated with Resolute Integrity and those treated with Xience, a prespecified propensity score-adjusted model was used for comparisons of Resolute Integrity to

Figure 3. The 12-month cumulative incidence of cardiovascular events with the Resolute Integrity in the PROPEL clinical-only cohort compared with Xience historical control. (A) TLF. (B) Clinically driven TLR. (C) Cardiac death or target vessel MI. (D) ARC definite or probable stent thrombosis. ARC, Academic Research Consortium; TLF, target lesion failure; TLR, target lesion revascularization.

Xience, including in the P-value for non-inferiority (and superiority) of Resolute Integrity to Xience. The following baseline variables were used for propensity score calculations: age, male sex, diabetes mellitus, prior MI, lesion length, preprocedure reference vessel diameter, and SYNTAX score.²⁶

All analyses were conducted on an intention-to-treat basis. Continuous parameters are presented as mean $\pm$ SD; nominal parameters as counts and percentages. The 12-month cumulative incidence of clinical events was assessed according to Kaplan-Meier estimates and compared with the Xience historical arm using the log-rank test. $P < 0.05$ was considered statistically significant. Analyses were performed using SAS software, version 9.1 or later (SAS Institute, Cary, NC, USA).

Results

The PROPEL trial enrolled 1,204 patients with coronary artery disease from 76 sites between February 2013 and September 2014. The first 905 patients were enrolled in the clinical-only cohort, and the remaining 299 patients in the routine angiographic cohort. Patient disposition is shown in **Figure 1**.

Table 1 provides baseline patient and lesion characteristics and acute success with Resolute Integrity in the clinical-only cohort compared with the Xience historical control.

Both cohorts were equally complex. Patients in the Resolute Integrity cohort were more likely to be older, have diabetes mellitus, a history of hypertension, hyperlipidemia, prior PCI, and longer lesions, but less likely to have prior MI, prior coronary artery bypass graft surgery, revascularization because of acute MI, and severely calcified lesions. Baseline patient characteristics of all PROPEL patients and those in the angiographic follow-up cohort are shown in **Table S1**.

Baseline lesion characteristics and acute success in all PROPEL patients and in the angiographic follow-up cohort are shown in **Table 2**. All lesions were successfully crossed (100% lesion success); device and procedural success rates with Resolute Integrity were 97.9% and 99.3%, respectively. At 10 months, in-segment and in-stent late lumen losses in the angiographic cohort were 0.16 ± 0.37 and 0.26 ± 0.4 mm, respectively (**Table 3**).

The primary endpoint, 12-month TLF in the clinical-only cohort compared with the Xience historical control, was 4.3% (34/800) vs. 8.5% (97/1,142); the upper bound of the 1-sided 95% confidence interval (CI) was -2.2% and less than the prespecified upper bound of 3.5% ($P < 0.001$ for non-inferiority; **Figure 2**).

Compared with Xience, Resolute Integrity was also associated with a lower rate of TVF, MACE, target vessel

Figure 4. The 12-month incidence of cardiovascular events in high-risk patients treated with Resolute Integrity in the PROPEL clinical-only cohort compared with historical control Xience. P values were adjusted by a prespecified propensity score model as defined in Methods. MACE, major adverse cardiac events; TLR, target lesion revascularization; TV-MI, target vessel myocardial infarction; TVF, target vessel failure. Stent thrombosis defined by Academic Research Consortium definite or probable stent thrombosis.

MI, and the composite of cardiac death and TV-MI (Table 4). The cumulative incidence of TLF and its components, clinically driven TLR, and cardiac death/target vessel MI, as well as ARC definite or probable ST, are shown in Figure 3.

TLF was low across complex subsets, including patients with diabetes mellitus, ST-segment MI, bifurcation lesions, and small vessel treatment (Figure S1). The 12-month incidence of TLF with Resolute Integrity in the clinical-only cohort compared with the Xience historical control was 5.4% vs. 9.0% (odds ratio, 0.6; 95% CI, 0.3–1.1) in patients with diabetes mellitus and 5.9% vs. 11.4% (odds ratio, 0.5; 95% CI, 0.2–1.0) in patients treated for a bifurcation lesion. Furthermore, 78% of the clinical-only cohort and 63% of the historical control cohort were considered high-risk patient populations, as defined in the Methods. In these high-risk patient populations at 12 months, Resolute Integrity was associated with a lower incidence of TLF compared with Xience (4.5% vs. 9.4%, $P<0.001$), as well as lower incidences of TVF, MACE, target vessel MI, and the composite cardiac death/TV-MI (Figure 4).

DAPT usage at 30 days, 6 months, and 12 months was 97%, 95%, and 79%, respectively. The 1-year ARC definite early ST was 0.3% (3/1,072). All 3 cases were definite ST before 30 days; no cases of ST occurred between 30 days and 12 months. The 12-month incidence of cardiovascular events was similar in patients treated in the clinical-only and angiographic cohorts (4.3% vs. 5.5%, $P=0.392$).

Discussion

The PROPEL study is the first large, prospective, multi-center study to investigate the long-term clinical outcomes of Resolute Integrity in a real-world patient population. The primary outcome, 12-month TLF, was 4.3% with Resolute Integrity vs. 8.5% with Xience ($\Delta=-4.2\%$, $P<0.001$ for non-inferiority). The low rate of 4.3% TLF in

PROPEL was driven by a very low rate of 0.2% for target vessel MI, compared with a TV-MI rate of 4.0% for Xience in the historical control. This difference could be attributed to differences in procedural technique between Japan and Europe, although this is speculative. In addition, TVF, MACE, and the composite cardiac death and target vessel revascularization were all lower with Resolute Integrity compared with the historical control Xience. This difference in cardiovascular outcomes was also observed in high-risk patients.

Lesion success in PROPEL with Resolute Integrity was 100%. The low in-hospital MI rate in PROPEL contributed to the improvement in procedural success, which was 99% with Resolute Integrity. This high procedural success is similar to that observed in other studies of Resolute Integrity, including the all-comer trial Deliverability of the Resolute Integrity Stent in All-Comer Vessels and Cross-over Stenting (DELIVER; 97.9%),²⁷ and An Evaluation of the Commercially Available Medtronic Resolute Integrity Zotarolimus-Eluting Coronary Stent System (RESOLUTE Integrity US; 98.2%).²⁸ Procedural success appeared to be higher than that observed with the previous-generation Resolute DES or with current-generation Xience DES, including in RESOLUTE All-Comers (94.6% and 94.2%, respectively).¹³

The 12-month TLF with Resolute Integrity in PROPEL remained low across complex subgroups and numerically lower than that observed with Xience in RESOLUTE All-Comers, including in the majority of complex subsets. It is often in these more complex patient subsets that improving lesion crossability and minimizing plaque abrasion during stent delivery are most important.

Furthermore, TLF with Resolute Integrity was similar in patients with non-insulin-dependent diabetes mellitus and those without diabetes mellitus, as well as in patients who presented with ST-segment elevation MI and those who did not. This has been observed with its predecessor

Resolute DES,^{29,30} and may in part be related to the non-thrombogenic BioLinx polymer used in both stents.¹⁷ The low rates of cardiovascular events in PROPEL may also be related to the Japanese operators, as Japanese operators are known to have high procedural success rates, including successful recanalization of chronic total occlusions of $\approx 90\%$ (even in low-volume centers).³¹

Study Limitations

The primary endpoint used a prespecified historical control. Although both populations were similarly complex, the PROPEL study was conducted in Japan, whereas the RESOLUTE All-Comers study was conducted in Europe and regional differences in procedural techniques and patient populations may have affected outcomes. Results were not adjusted for differences in procedural technique such as IVUS-guided PCI vs. angio-guided PCI, use of post-dilatation, or amount of stent inflation pressure applied, and these differences may have influenced outcomes.

Conclusions

The PROPEL study is the first large, prospective, multicenter study to investigate the long-term clinical outcomes of the Resolute Integrity DES in a real-world patient population. Performance of the Resolute Integrity stent was non-inferior to the benchmark Xience DES used as historical comparator. Lesion and procedural success rates with Resolute Integrity were 100% and 99%, respectively. Cardiovascular events with Resolute Integrity in PROPEL were low across complex subgroups.

Conflict of Interest Statement

S.O. has consultancy agreements with Asahi Intecc and Goodman Nipro, and receives speaker fees from Boston Scientific and Abbott. All other authors have nothing to disclose. All authors have approved the final article.

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Supplementary Files

Supplementary File 1

Appendix S1. PROPEL Principal Investigators and Affiliations

Figure S1. Forrest plot for the comparison of Resolute Integrity in the PROPEL clinical-only cohort compared with Xience historical control in 12-month target lesion failure across patient subsets.

Table S1. Baseline characteristics of subjects in PROPEL, stratified by all patients and the angiographic cohort

Please find supplementary file(s);
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