Safety and Efficacy of New-Generation Drug-Eluting Stents in Women at High Risk for Atherothrombosis

From the Women in Innovation and Drug-Eluting Stents Collaborative Patient-Level Pooled Analysis

Gennaro Giustino, MD; Usman Baber, MD, MSc; Olga Salianski; Samantha Sartori, PhD; Gregg W. Stone, MD; Martin B. Leon, MD; Melissa Aquino, MSc; Giulio G. Stefanini, MD, PhD; P. Gabriel Steg, MD, PhD; Stephan Windecker, MD, PhD; Monica O' Donoghue; William Wijns, MD; Patrick W. Serruys, MD, PhD; Marco Valgimigli, MD, PhD; Marie-Claude Morice, MD; Edoardo Camenzind, MD; Giora Weisz, MD; Pieter C. Smits, MD; David Kandzari, MD; Clemens Von Birgelen, MD; George D. Dangas, MD, PhD; Jin Y. Cha; Soren Galatius, MD; Raban V. Jeger, MD; Takeshi Kimura, MD; Ghada W. Mikhail, MD; Dipti Itchhaporia, MD; Laxmi Mehta, MD; Rebecca Ortega, MD; Hyo-Soo Kim, MD; Adnan Kastrati, MD; Philippe Genereux, MD; Alaide Chieffo, MD; Roxana Mehran, MD

Background—The safety and efficacy of new-generation drug-eluting stents (DES) in women with multiple atherothrombotic risk (ATR) factors is unclear.

Methods and Results—We pooled patient-level data for women enrolled in 26 randomized trials. Study population was categorized based on the presence or absence of high ATR, which was defined as having history of diabetes mellitus, prior percutaneous or surgical coronary revascularization, or prior myocardial infarction. The primary end point was major adverse cardiovascular events defined as a composite of all-cause mortality, myocardial infarction, or target lesion revascularization at 3 years of follow-up. Out of 10 449 women included in the pooled database, 5333 (51%) were at high ATR. Compared with women not at high ATR, those at high ATR had significantly higher risk of major adverse cardiovascular events (15.8% versus 10.6%; adjusted hazard ratio: 1.53; 95% confidence interval: 1.34–1.75; P=0.006) and all-cause mortality. In high-ATR risk women, the use of new-generation DES was associated with significantly lower risk of 3-year major adverse cardiovascular events (adjusted hazard ratio: 0.69; 95% confidence interval: 0.52–0.92) compared with early-generation DES. The benefit of new-generation DES on major adverse cardiovascular events was uniform between high-ATR and non–high-ATR women, without evidence of interaction ($P_{interaction}$=0.14). At landmark analysis, in high-ATR women, stent thrombosis rates were comparable between DES generations in the first year, whereas between 1 and 3 years, stent thrombosis risk was lower with new-generation devices.

Conclusions—Use of new-generation DES even in women at high ATR is associated with a benefit consistent over 3 years of follow-up and a substantial improvement in very-late thrombotic safety. **(*Circ Cardiovasc Interv*. 2016;9:e002995. DOI: 10.1161/CIRCINTERVENTIONS.115.002995.)**

Key Words: drug-eluting stents ■ high atherothrombotic risk ■ myocardial infarction ■ percutaneous coronary intervention ■ women

Received July 14, 2015; accepted December 15, 2015.

From the The Zena and Michael A. Wiener Cardiovascular Institute, Interventional Cardiovascular Research and Clinical Trials Center, Icahn School of Medicine at Mount Sinai, New York City, NY (G.G., U.B., O.S., S.S., M.A., M.O., G.D.D., J.Y.C., R.M.); Division of Cardiology, Columbia University Medical Center, New York City, NY (G.W.S., M.B.L., P.G.); Department of Cardiology, Bern University Hospital, Bern, Switzerland (S.W.); Department of Cardiology, ErasmusMC, Rotterdam, The Netherlands (P.W.S.); Department of Cardiology and Cardiovascular Surgery, Institut Cardiovasculaire Paris Sud, France (M.-C.M.); Cardiovascular Center Aalst, Onze-Lieve-Vrouwziekenhuis Ziekenhuis, Aalst, Belgium (W.W.); Deparment of Cardiology, Institut Lorrain du Coeur et des Vaisseaux (ILCV) University Hospital Nancy–Brabois Vandoeuvre-lès-Nancy France (E.C.); Département Hospitalo Universitaire Fibrose, Inflammation et REmodelage, Assistance Publique-Hôpitaux de Paris, Université Paris Diderot, INSERM U114, Paris, France (P.G.S.); Maasstad Hospital, Rotterdam, Netherlands (P.C.S.); Department of Cardiology, Piedmont Heart Institute, Atlanta, GA (D.K.); Department of Cardiology, Thoraxcentrum Twente, Enschede, Netherlands (C.V.B.); Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark (S.G.); Department of Cardiology, University Hospital Basel, Basel, Switzerland (R.V.J.); Department of Cardiology, Kyoto University Graduate School of Medicine, Kyoto, Japan (T.K.); Department of Cardiology, Imperial College Healthcare NHS Trust, London, UK (G.W.M.); Department of Cardiology, Hoag Memorial Hospital Presbyterian, Newport Beach, CA (D.I.); Department of Cardiology, Ohio State University Medical Center, Columbus, OH (L.M.); Society of Cardiovascular Angiography and Interventions, Washington, DC (R.O.); Department of Cardiology, Seoul National University Main Hospital, Seoul, Korea (H.-S.K.); Department of Cardiology, University of Ferrara, Ferrara, Italy (M.V.); Department of Cardiology, Herzzentrum, Munich, Germany (A.K.); Cardio-Thoracic Department, San Raffaele Scientific Institute, Milan, Italy (A.C.); Department of Cardiology, Shaare Zedek Medical Center, Jerusalem, Israel, and Columbia University Medical center, New York, NY (G.W.); and Division of Clinical and Interventional Cardiology, Humanitas Research Hospital, Rozzano, Milan, Italy (G.G.S.).

The Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.115.002995/-/DC1.

Correspondence to Roxana Mehran, MD, The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, NY 10029. E-mail Roxana.Mehran@mountsinai.org

WHAT IS KNOWN

- Concomitance of multiple atherothrombotic risk factors enhance propensity for coronary ischemic events and mortality.
- Increased platelet inhibition is beneficial in patients at high risk for atherothrombotic events. However, whether the improved biocompatibility and antithrombotic properties of new-generation drug-eluting stent are preserved in women at high atherothrombotic risk is unknown.

WHAT THE STUDY ADDS

- In women at high atherothrombotic risk, compared with early-generation drug-eluting stent, new-generation devices are associated with preserved safety and efficacy over 3 years of follow-up and with a substantial benefit in very-late (>1 year) stent-related thrombotic safety.
- In women not at high atherothrombotic risk, new-generation drug-eluting stents were associated with an exceedingly low risk of very-late (>1 year) stent thrombosis at 3 years of follow-up.

Atherothrombosis is a life-threatening condition in which rupture of a high-risk plaque can lead to thrombosis and occlusion of an artery, in turn causing symptoms of peripheral ischemia, stroke, or acute coronary syndrome.[1] Currently, atherothrombotic disorders of the coronary, cerebrovascular, and peripheral arterial vasculature are the leading cause of mortality worldwide. In fact, according to the American Heart Association, over 1.1 million Americans in 2010 were hospitalized with acute coronary syndrome.[1,2] Importantly, about 488 000 of these patients were women.[2] Women also constitute about one third of all patients treated with percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation.[2] However, women have been underrepresented in randomized controlled trials (RCTs) that investigated the safety and efficacy of DES. In the 2011 Food and Drug Administration's guidance document, gender disparities in RCTs investigating medical devices were identified and addressed. In response to the recommendations expressed by the Food and Drug Administration, the Society for Cardiovascular Angiography and Interventions' Women in Innovation Initiative organized a Gender Data Forum in which the outcomes of DES in women were addressed. This led to the creation and analysis of the present large individual female patient–level pooled data set from existing randomized trials of DES.

Although trials investigating pharmacotherapies targeting key molecular and cellular players in the pathogenesis of arterial thrombosis have been conducted in patients with multiple atherothrombotic risk (ATR) factors,[3–5] to date, few data are available regarding the relative safety and efficacy of new-generation DES in such a high-risk population, especially of female sex. With the hypothesis that presence of durable multiple ATR factors might attenuate the benefits associated with new-generation DES, in the present patient-level pooled analysis of RCTs, we sought to evaluate the prognostic impact of a study-defined high-ATR in women undergoing PCI and the safety and efficacy of new-generation DES, compared with early-generation, in women with or without high ATR.

Methods

Study Design and Population

The rationale of the present patient-level pooled database, list of trials, analytic strategies, and prespecified end points has been previously reported.[6] Briefly, female participants from 26 RCTs were pooled: RAVEL (The Initial Double-Blind Drug-Eluting Stent vs Bare-Metal Stent Study), SIRIUS (Study of Sirolimus-Coated BX VELOCITY Balloon-Expandable Stent in Treatment of de Novo Native Coronary Artery Lesions), E-SIRIUS (The Study of the BX VELOCITY Stent in Patients With De Novo Coronary Artery Lesions), C-SIRIUS (The Study of the BX Velocity Stent in the Treatment of De Novo Artery Lesions), TAXUS-I (Randomized, Double-Blind Trial on a Slow-Release Paclitaxel-Eluting Stent for De Novo Coronary Lesions), TAXUS-II SR (A Randomized Study to Assess the Effectiveness of Slow- and Moderate- Release Polymer-Based Paclitaxel-Eluting Stents for De Novo Coronary Artery Lesions), TAXUS-IV (Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent), TAXUS-V (A Randomized, Double-Blind Trial to Assess TAXUS Paclitaxel-Eluting Coronary Stents, SR Formulation, in the Treatment of De Novo Coronary Lesions), SIRTAX (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization), ENDEAVOR II (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions), ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions), ENDEAVOR-IV (Randomized Comparison of Zotarolimus-Eluting and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease), SPIRIT II (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions), SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions), SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions), BASKET-PROVE (Evaluation of Late Clinical Events After Drug-Eluting Versus Bare-Metal Stents in Patients at Risk: Basel Stent Kosten Effektivitäts Trial - Prospective Validation Examination Part II), COMPARE I (A Randomized Controlled Trial of Everolimus Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice), COMPARE II (Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent), EXCELLENT (The Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting), RESET (Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation), RESOLUTE AC (Randomized, Two-Arm, Non-Inferiority Study Comparing Endeavor-Resolute Stent With Abbot Xience-V Stent), TWENTE (The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting Stent Study in Twente), LEADERS (A Randomized Comparison of a Biolimus-Eluting Stent With a Sirolimus-Eluting Stent for Percutaneous Coronary Intervention), ISAR TEST 4 (Prospective, Randomized Trial of 3-Limus Agent-Eluting Stents With Different Polymer Coatings), PRODIGY (Prolonging Dual Antiplatelet Treatment in Patients With Coronary Artery Disease After Graded Stent-Induced Intimal Hyperplasia Study), and PROTECT (Patient Related Outcomes With Endeavor Versus Cypher Stenting Trial) (full reference list included in the Appendix

Table 1. Baseline Clinical and Angiographic Characteristics According to High-Atherothrombotic Risk Status

	High-ATR (N=5333; 51.0%)	No High-ATR (N=5116; 49.0%)	*P* Value
Age	67.9±10.3	66.5±10.9	<0.0001
BMI	29.2±6.3	27.2±5.3	<0.0001
Cardiac risk factors			
Diabetes mellitus	3294 (61.8%)	0 (0.0%)	<0.0001
IDDM	1053 (32.0%)	…	…
Arterial hypertension	4403 (82.6%)	3478 (68.0%)	<0.0001
Hypercholesterolemia	3982 (74.8%)	3060 (60.0%)	<0.0001
Current or former smoking	1225 (23.1%)	1587 (31.1%)	<0.0001
Family history of CAD	1918 (39.0%)	1885 (39.1%)	0.91
Previous MI	1915 (36.1%)	0 (0.0%)	<0.0001
Previous PCI	2136 (41.0%)	0 (0.0%)	<0.0001
Previous CABG	522 (9.8%)	0 (0.0%)	<0.0001
Clinical presentation			<0.0001
Stable angina	3147 (60.9%)	2613 (52.6%)	
Unstable angina	1204 (23.3%)	993 (20.0%)	
NSTEMI	618 (12.0%)	779 (15.7%)	
STEMI	196 (3.8%)	583 (11.7%)	
LVEF, %	54.4±17.2	56.8±17.5	<0.0001
Angiographic characteristics			
Number of lesions treated	1.30±0.62	1.27±0.59	0.04
Number of stents implanted	1.55±0.94	1.52±0.90	0.04
Mean stent diameter, mm	3.0±0.4	3.0±0.4	<0.0001
Total stent length, mm	30.1±19. 6	29.0±18.4	0.004
Type B2/C lesion	2804 (64.6%)	2447 (61.5%)	0.003
Moderate/severe calcifications	900 (26.9%)	722 (23.8%)	0.005
Bifurcation lesion	498 (19.9%)	456 (19.4%)	0.69
Type of stent implanted			<0.0001
Early-generation stent	2146 (40.2%)	2025 (39.6%)	
New-generation stent	3187 (59.8%)	3091 (60.4%)	

Results reported as n (%) or mean±standard deviation as appropriate. ATR indicates atherothrombotic risk; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; DES, drug-eluting stent; IDDM, insulin-dependent diabetes mellitus; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; SA, stable angina; STEMI, ST-segment–elevation myocardial infarction; and UA, unstable angina.

in the Data Supplement). Characteristics of the RCTs included in the present study are summarized in the Table I in the Data Supplement. All the included RCTs were performed between 2000 and 2013. The study population was stratified into 2 categories based on the presence or absence of high ATR (Table 1). Women who received a bare-metal stent were excluded from this analysis. ATR was defined as the composite of history of diabetes mellitus (DM), previous revascularization (PR; defined as previous PCI or previous coronary artery bypass graft), or previous myocardial infarction (PMI). The rationale of such definition is based on the criteria used in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)[3] according to the available clinical variables included in the pooled data set. Moreover, each one of these risk factors previously demonstrated to be associated with substantial increased risk for adverse events in patients undergoing PCI.[7–9]

All trials included in our analysis complied with the provisions of the Declaration of Helsinki, and the institutional review board at each study center approved the study protocols. All patients provided written informed consent for participation in each study.

Drug-Eluting Stents

The following DES have been included in the present analysis: sirolimus-eluting stents (Cypherand Cordis, Johnson & Johnson, Miami Lakes, FL), paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, MA), everolimus-eluting stents (Xience, AbbottVascular, Santa Clara, CA; Promus, Boston Scientific), zotarolimus-eluting stents (Endeavor, Medtronic, Santa Rosa, CA; Resolute, Medtronic), biolimus-eluting stents with biodegradable polymer coating (Biomatrix, Biosensors, Newport Beach, CA; Nobori, Terumo, Tokyo, Japan), and sirolimus-eluting stents with biodegradable polymer coating (Yukon, Translumina, Hechingen, Germany).

Coronary stents used among trials were classified as early-generation DES (including sirolimus- and paclitaxel-eluting stents) and new-generation DES (including everolimus and zotarolimus stents

with durable polymer and biolimus- and sirolimus-eluting stents with biodegradable polymer).

Study Objectives and End Points Definitions

The objectives of the present study were (1) to characterize the impact of multiple ATR factors on outcomes in women undergoing PCI with DES and (2) to evaluate the safety and efficacy of new-generation DES, compared with earlier generation, in women at high ATR. The primary end point of the current study was the risk of major adverse cardiac events (MACE). MACE was defined as the composite of all-cause mortality, myocardial infarction (MI), or target-lesion revascularization. Additional end points were the individual components of MACE, cardiac mortality, definite or probable stent thrombosis (ST), and the composite of all-cause mortality, MI, or definite or probable ST. The clinical end point definitions used across trials are detailed in Table II in the Data Supplement.

Statistical Analysis

All patient-level data were aggregated and combined as one data set on a prespecified extraction sheet. Baseline clinical, demographic, and procedural characteristics of the study groups were reported as mean±standard deviation for continuous variables and as proportions for categorical variables. Continuous variables were compared with student t test. Categorical variables were compared with χ^2 test. Cumulative event rates in the study groups were calculated with the Kaplan–Meier method and compared with the log-rank test. For these analyses, the total follow-up was defined as the time from index procedure until death, last follow-up date, or 3 years, whichever came first. Additionally, we performed Kaplan–Meier analyses in the landmark periods of zero to 1 year and of 1 to 3 years to evaluate the impact of DES generation on thrombotic end points at different time periods. The independent associations between high ATR, stent generation, and outcomes were assessed with the Cox proportional hazards models that included a frailty term (γ) to assess random effects in the trials. Frailties are the unmeasured factors that affect trial-specific baseline risk and are distributed as γ random variables with a mean of 1 and variance θ. The variance parameter was interpreted as a metric of heterogeneity in baseline risk between trials. In the adjusted analysis evaluating the impact of high ATR on outcomes, no high ATR was the reference category. For the DES-level analysis, early-generation DES was the reference category. Multivariable models included covariates that significantly differed at univariate analysis and those deemed clinically relevant from previous studies (without including variables that are intrinsically part of the composite ATR definition). The full list of covariates included in the multivariable models is listed in the footnotes of the tables. The proportionality assumption was verified by means of scaled Schoenfeld residual. Multicollinearity was evaluated by means of visual inspection of correlation matrix and estimation of the variance inflation factor, with >10 used as a threshold to define significant multicollinearity. For the DES-level analysis, the consistency of the effect of new-generation DES in women with or without high ATR was evaluated with formal interaction test. We judged P values of <0.05 to be significant, and all analyses were done with SAS software.

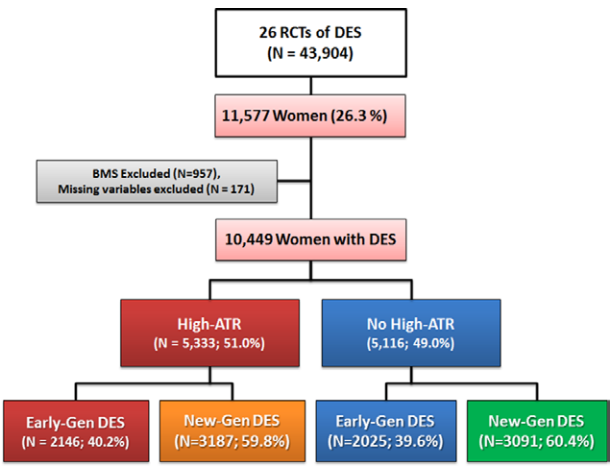


Figure 1. Study population flow diagram. ATR indicates atherothrombotic risk; BMS, bare metal stent; DES, drug-eluting stent; and RCT, randomized controlled trial.

Results

Baseline Characteristics

Out of 10449 women included in the pooled database, 5333 (51%) were at high ATR (Figure 1). Clinical characteristics according to high ATR are reported in Table 1. Women with high ATR were older, had higher body mass index, and had greater prevalence of arterial hypertension and hypercholesterolemia. Patterns of clinical presentation significantly differed between groups: women at high ATR had more stable phenotypes and women without high ATR had higher prevalence of MI presentation. Angiographic and procedural data are reported in Table 1. Women with high ATR had a higher number of lesions treated, stents implanted, American College of Cardiology/American Heart Association type B2/C lesions, moderate or severe calcifications, and greater total stent length.

Impact of High ATR Status on 3-Year Clinical Outcomes

Unadjusted and adjusted clinical outcomes according to high-ATR status are reported in Table 2. A significantly higher crude rate of MACE was observed in women with versus without high ATR (Figure 2A; 15.8 % versus 10.6%; P<0.0001). Women with high ATR also had higher rates of all-cause mortality (Figure 2B), cardiac mortality, MI, target-lesion revascularization, definite or probable ST, and the composite of all-cause mortality, ST, or MI.

Following multivariable adjustment, high ATR status was independently associated with higher risk of MACE (adjusted hazard ratio [HR]: 1.53; 95% confidence interval [CI]: 1.34–1.75; P<0.0001), all-cause mortality (adjusted HR: 2.10; 95% CI: 1.66–2.66; P<0.0001), cardiac mortality (adjusted HR: 2.35; 95% CI: 1.71–2.23; P<0.0001), MI (adjusted HR: 1.32; 95% CI: 1.06–1.64; P=0.01), target-lesion revascularization (adjusted HR: 1.49; 95% CI: 1.22–1.81; P<0.0001), ST (adjusted HR: 2.23; 95% CI: 1.42–3.49; P<0.0001), and the composite of all-cause mortality, MI, or ST (adjusted HR: 1.58; 95% CI: 1.34–1.85; P<0.0001).

Event rates for MACE and all-cause mortality according to the component of high ATR definition are illustrated in Figure 3. Following multivariable adjustment, among the individual component of high ATR, only DM was associated with higher risk of MACE (adjusted HR: 1.57; 95% CI: 1.28–1.93; P<0.0001). Conversely, PR and PMI had no independent effect on MACE risk (adjusted HR: 1.19, 95% CI: 0.89–1.60; P=0.22; and adjusted HR: 1.11, 95% CI: 0.77–1.58; P=0.58, respectively). Similar findings were observed for all-cause mortality, with DM independently associated with this outcome (adjusted HR: 2.20; 95% CI: 1.65–2.93; P<0.0001), whereas PR and PMI were not. The combination of ≥2 risk factors was associated with the highest risk of MACE (adjusted

Table 2. Unadjusted and Adjusted 3-Year Clinical Outcomes According to High-Atherothrombotic Risk Status

	High-ATR (N=5333; 51.0%)	No High-ATR (N=5116; 49.0%)	*P* Value*	Adjusted HR (95% CI)†	*P* Value‡
All-cause mortality	310 (5.8)	175 (3.4)	<0.0001	2.10 (1.66–2.66)	<0.0001
Cardiac mortality	183 (4.1)	90 (2.1)	<0.0001	2.35 (1.71–3.23)	<0.0001
Myocardial infarction	306 (5.7)	203 (4.0)	<0.0001	1.32 (1.06–1.64)	0.01
TLR	379 (7.1)	245 (4.8)	<0.0001	1.49 (1.22–1.81)	<0.0001
Def. or prob. ST	53 (1.0)	33 (0.7)	0.049	2.23 (1.42–3.49)	<0.0001
MACE	845 (15.8)	543 (10.6)	<0.0001	1.53 (1.34–1.75)	<0.0001
All-cause mortality or ST or MI	572 (10.7)	360 (7.0)	<0.0001	1.58 (1.34–1.85)	<0.0001

ATR indicates atherothrombotic risk; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; ST, stent thrombosis; and TLR, target-lesion revascularization.

*Log-rank *P* value.

†Variables included in the model were age, body mass index, hypertension, dyslipidemia, family history of CAD, smoking, presentation with an acute coronary syndrome, stent generation, serum creatinine, stent length, and type B2 or C lesions. Hazard ratio expressed with No High-ATR as the reference group.

‡Wald *P* value.

HR: 1.78; 95% CI: 1.46–2.16; *P*<0.0001) and all-cause mortality (adjusted HR: 2.38; 95% CI: 1.80–3.13; *P*<0.0001).

Early- Versus New-Generation DES in Women at High ATR

Three-year outcomes according to ATR status and DES generation are reported in Table 3 and Figure 4. In women with high ATR, the use of new-generation DES was associated with significantly lower risk of MACE at 3 years (adjusted HR: 0.79; 95% CI: 0.63–0.99) compared with early-generation DES (Table 3). As well, compared with early-generation DES, use of new-generation devices was associated with a significant benefit in cardiac mortality (adjusted HR: 0.52; 95% CI: 0.31–0.88), MI (adjusted HR: 0.68; 95% CI: 0.47–0.98), and the composite of all-cause mortality, ST, or MI (adjusted HR: 0.69; 95% CI: 0.52–0.92). The effects of new-generation DES on outcomes were uniform between high-ATR and non–high-ATR women, without evidence of interaction. Additionally, the effect of new-generation DES on the risk of MACE (Figure I in the Data Supplement) and death, MI, or ST (Figure II in the Data Supplement) were uniform across markers of anatomical and procedural complexity, in a magnitude that was overall similar with the one observed between high-ATR and non-ATR groups.

Kaplan–Meier analyses in the landmark periods for thrombotic end points according ATR status and DES generation are illustrated in Figure 5A (composite of all-cause mortality, MI, or ST) and 5B (ST). A significantly lower risk of all-cause mortality, MI, or ST and ST was observed within both zero and 1 year and between 1 and 3 years with new-generation DES in women not at high ATR. Of note, in women not at high ATR, rates of ST were low within both the first year (0.5%) and between 1 and 3 years (0.1%). In women at high ATR, rates of ST in the first year with new-generation DES approximated those observed with early-generation devices; conversely, after 1 year, new-generation DESs were associated with improved very-late ST safety compared with early-generation DES (Figure 5B).

Discussion

To the best of our knowledge, this is the first large report with patient-level data from RCTs investigating the safety and efficacy of early- and new-generation DES in women at high risk for atherothrombosis undergoing PCI. The main findings of our study are the following: (1) the presence of multiple ATR factors is associated with increased long-term risk of MACE and mortality after DES implantation in women; among these,

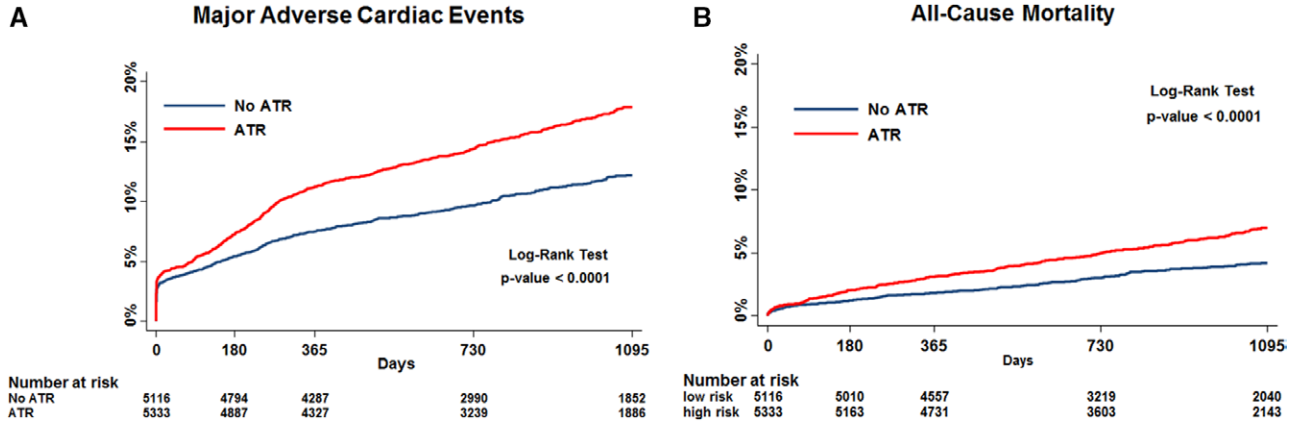


Figure 2. Cumulative Kaplan–Meier curves for major adverse cardiac events (**A**) and all-cause mortality (**B**) at 3 years in women according to ATR status. *P* value from log-rank test. ATR indicates atherothrombotic risk.

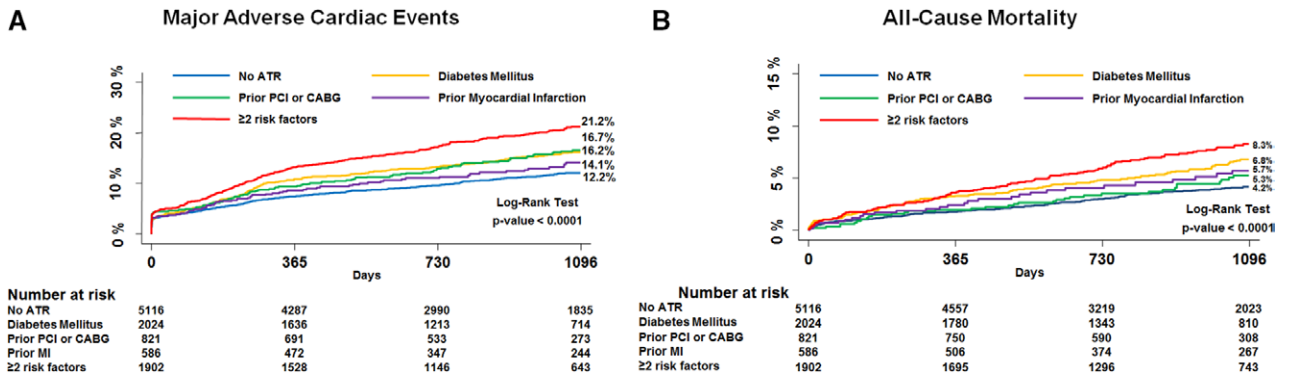


Figure 3. Cumulative Kaplan–Meier curves for major adverse cardiac events (**A**) and all-cause mortality (**B**) at 3 years in women according to the atherothrombotic risk factor. *P* value from log-rank test. ATR indicates atherothrombotic risk; CABG, coronary artery bypass graft; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

DM was the only one independently associated with higher MACE and mortality risk; combination of ≥2 risk factors confers an additive hazard on long-term adverse events; (2) compared with early-generation DES, use of new-generation DES is associated with consistent benefit on adverse outcomes in women, irrespective of ATR status; in particular, in high-ATR women, antithrombotic properties of new-generation devices seem to be more evident between one and three years, rather within the first year post-PCI; (iii) women not at high-ATR treated with new-generation DES had low risk of very-late ST at 3 years of follow-up.

Although early-generation DES significantly improved the efficacy of PCI compared with bare metal stent, new-generation platforms substantially enhanced the safety of intracoronary stent implantation by mitigating the risk of late and very-late platform thrombosis.[10] Concerns regarding the unrestricted use of DES were mainly because of the higher risk of ST observed in high-risk patients or high-risk coronary lesions.[11] Although studies, such as the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE),[12] a substudy from CHARISMA in high-risk patients,[13] and others,[4,5] demonstrated an improved anti-ischemic efficacy with lower risk of adverse cardiac events in high-ATR patients with addition of higher potency antiplatelet agents, such evidence with new-generation DES, and in particular in women, is poor. In the present analysis, we sought to expand the existing evidence by evaluating the impact of high ATR on clinical outcomes in women undergoing PCI with DES and by investigating whether the benefits of new-generation DES are maintained in women with and without high-ATR status.

ATR and Outcomes in Women Undergoing PCI

Study-defined high ATR was associated with greater coronary artery disease (CAD) severity and complexity and a substantial crude and independent increased risk of MACE, mortality, and each single ischemic end point in women after DES implantation. Among the available variables in the pooled data set, we opted to use 3 well-defined risk factors for future adverse events (DM, PR, and PMI) to identify patients at high ATR, given the solid supporting literature and their pathobiological direct or indirect role in atherothrombosis.[3–5,13] Among the available baseline clinical variables, we did not opt to include clinical presentation within ATR definition because we previously demonstrated that most of the risk in women associated with increased acuteness and severity of CAD across its clinical spectrum appears to be confined within 1 year to then decay over time.[14] Conversely, the included clinical variables might have a more durable effect on the risk of adverse events after

Table 3. Three-Year Clinical Outcomes Between Early- and New-Generation Drug-Eluting Stents According to High-Atherothrombotic Risk Status

	High-ATR Early-Gen DES (N=2146)	High-ATR New-Gen DES (N=3187)	High-ATR Adjusted HR (95% CI)*	No High-ATR Early-Gen DES (N=2025)	No High-ATR New-Gen DES (N=3091)	No High-ATR Adjusted HR (95% CI)*	*P* for Interaction
All-cause mortality	143 (9.6)	167 (5.2)	0.69 (0.47–1.02)	82 (4.1)	93 (3.0)	0.86 (0.47–1.56)	0.88
Cardiac mortality	89 (9.5)	94 (3.6)	0.52 (0.31–0.88)	40 (2.2)	50 (1.9)	0.73 (0.33–1.61)	0.53
Myocardial infarction	133 (6.2)	173 (5.4)	0.68 (0.47–0.98)	100 (4.9)	103 (3.3)	0.82 (0.48–1.39)	0.16
TLR	170 (7.9)	209 (6.6)	1.04 (0.74–1.46)	124 (6.1)	121 (3.9)	0.48 (0.27–0.84)	0.13
Def. or prob. ST	29 (1.4)	24 (0.8)	0.64 (0.25–1.59)	24 (1.8)	9 (0.3)	0.21 (0.03–1.36)	0.09
MACE	375 (17.5)	470 (14.8)	0.79 (0.63–0.99)	261 (12.9)	282 (9.1)	0.68 (0.48–0.96)	0.14
All-cause mortality, MI or ST	253 (11.8)	319 (10.0)	0.69 (0.52–0.92)	175 (8.6)	185 (6.0)	0.84 (0.56–1.25)	0.16

ATR indicates atherothrombotic risk; CAD, coronary artery disease; CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; ST, stent thrombosis; and TLR, target lesion revascularization.

*Variables included in the model were age, body mass index, hypertension, dyslipidemia, family history of CAD, smoking, presentation with an acute coronary syndrome, serum creatinine, stent length, and type B2 or C lesions. Hazard ratio expressed with early-generation DES as the reference group.

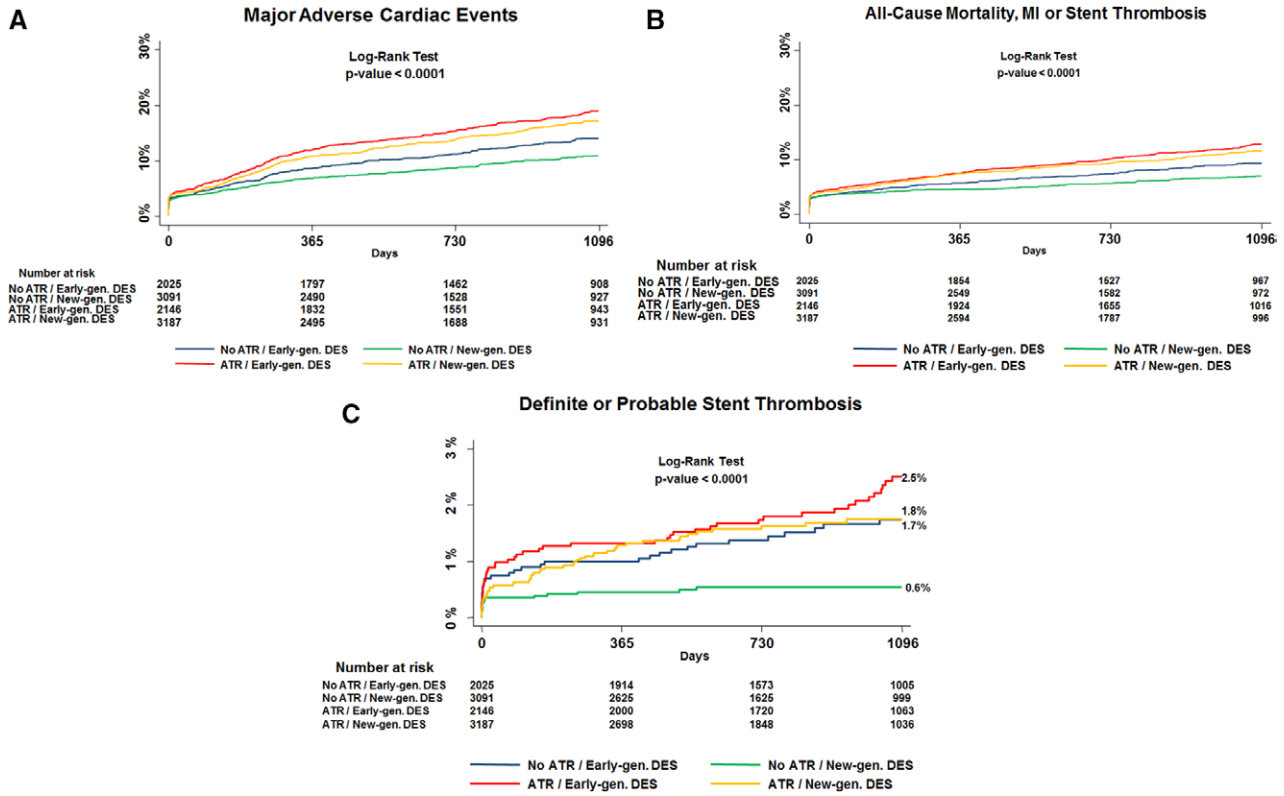


Figure 4. Cumulative Kaplan–Meier curves for major adverse cardiac events (**A**), the composite of all-cause mortality, myocardial infarction (MI), or stent thrombosis (**B**), and definite or probable stent thrombosis (**C**) at 3 years according to atherothrombotic risk status and drug-eluting stent generation. *P* value from log-rank test. ATR indicates atherothrombotic risk; and DES, drug-eluting stent.

PCI. We did not include smoking status because the definition of current smoking was not available and because the relationship between smoking and adverse outcomes is uncertain.[15] However, although the combination of these risk factors showed an additive effect on the risk of adverse events, only DM exhibited an increased and independent risk on MACE and mortality. The lack of independent effect of PR and PMI might be related to the fact that these 2 clinical variables are a reflection of the burden and severity of CAD rather than a direct mediator of the overall clinical risk. Although DM is directly involved in the pathogenesis of chronic kidney disease, endocrine dysfunction, increased thrombogenicity, peripheral arterial disease, and cerebrovascular disease,[16] the nature of the crude relationship between PR and PMI with adverse outcomes is most likely correlative rather than causative.

New-Generation DES in Women at High Risk for Atherothrombosis

By optimizing vascular biocompatibility, endothelialization with strut coverage, and drug release kinetic, compared with early-generation DES, new-generation DES significantly improved the late and very-late safety of intracoronary DES implantation.[10]

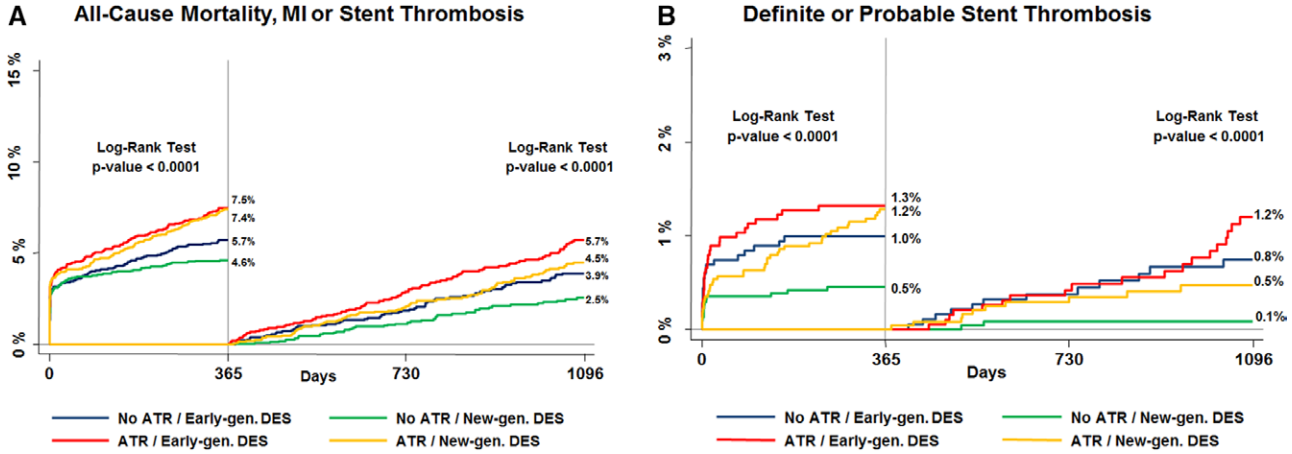


Figure 5. Kaplan–Meier curves for the composite of all-cause mortality, myocardial infarction (MI), or definite or probable stent thrombosis (**A**) and definite or probable stent thrombosis (**B**) in the landmark period of 0 to 1 year and 1 to 3 years in women treated with early- or new-generation drug-eluting stents (DES) according to ATR status. *P* value from log-rank test. ATR indicates atherothrombotic risk.

However, whether these benefits are maintained in the high-risk patient subset, in particular of female sex, is to date unclear. In women at high ATR, at 3 years, we observed a significant benefit with new-generation DES across all the studied ischemic outcomes, including cardiac mortality. Moreover, when we looked at the relative temporal distribution of event rates through 3 years, most of the stent-related thrombotic benefit was confined to the very-late period (1 to 3 years). In fact, the benefits of new-generation DES over early-generation DES in high-ATR women appear to be related to a substantial improvement in the very-late safety, whereas the event rates remain high early after PCI in this patient subset. Notably, the rates of ST were exceedingly low in women not at high ATR, especially between 1 and 3 years (0.1%). These findings have several important clinical implications: (1) in a contemporary practice with new-generation DES, women with CAD at lower risk for atherothrombosis might not benefit from prolonged (beyond 6 months or 1 year) dual antiplatelet therapy to prevent stent-related thrombotic complications; instead, these would expose such patients to an unnecessary bleeding and possibly mortality risk[17,18]; (2) conversely, women with high ATR, even with new-generation DES, remain at high risk for stent-related ischemic complications in the first year after PCI, suggesting that completion of at least 1 year of a regimen of dual antiplatelet inhibition might be appropriate in this patient subset in presence of low risk of bleeding. Considering that the presence of chronic ATR factors yields a constant risk over time to develop coronary thrombotic events (both stent- and non–stent-related),[19] the benefits associated with use of new-generation DES in this high-risk population are more likely to be observed over long-term follow-up rather than early after PCI. Therefore in presence of a favorable efficacy (antiischemic) and safety (prohemorrhagic) trade-off, high-ATR women might benefit from more potent and prolonged (>1 year) platelet inhibition which should be applied with the rationale of preventing cerebrovascular, peripheral, and non–DES-related coronary atherothrombotic events, rather than those occurring within the coronary vascular segment where a new-generation DES has been implanted.

Limitations

Notwithstanding our findings rely on individual patient-level, high-quality data from prospective, randomized trials with data monitoring and event adjudication by clinical event committees, several limitations have to be disclosed. First, atherothrombosis is a systemic disease so other clinical variables characterize this condition; however, important clinical variables, such as documented cerebrovascular disease, documented symptomatic peripheral arterial disease, carotid artery disease, diabetic nephropathy (baseline serum creatinine was available only in half of the study population), and uncontrolled arterial hypertension or hypercholesterolemia, were not available in the pooled data set; therefore, our study-defined population is more likely a high-cardiac-ATR rather than a high-systemic-ATR; however, the benefits of new-generation DES would be cardiac in nature as opposed to an antiplatelet agent that would confer a systemic effect and, therefore, acting also on noncoronary arterial vasculature. Second, some trials included in the analysis were performed more than a decade ago, during which clinical practice and device technology changed. To reduce the trial effect on outcomes, we included trial as a random effect in our adjusted analysis. Third, patient population across trials was heterogeneous; early trials focused only on stable CAD with simple lesion, whereas most recent trials had a tendency to include more complex patients and lesions subsets. Fourth, the exclusion of male participants from this study precludes sex-specific analysis, limiting the external validity of our findings. Fifth, this has to be considered as a post hoc analysis from RCTs not designed to specifically assess DES outcomes in women with high ATR. To overcome this limitation, we carried out a rigorous multivariable adjustment. However, as in any nonrandomized study, our findings are subject to residual confounding on the effect estimates.

Conclusions

Multiple risk factors for atherothrombosis are common in women with CAD undergoing PCI with DES and are associated with a substantial increased risk of MACE and mortality. Compared with early-generation DES, newer-generation DES are associated with a significantly improved safety and efficacy in women at high ATR at 3 years after PCI. Of note, in women at high ATR, the thrombotic benefit of new-generation DES appeared more evident in the very-late period rather than within 1 year after PCI. The rates of ST with new-generation DES in women not at high-ATR were low ≤3 years of follow-up. The results of the present patient-level pooled analysis underscore the significant benefits, and their temporal distribution, of new-generation DES in this high-risk subset of patients previously underrepresented in RCTs.

Acknowledgments

The Gender Data Forum was sponsored by the Women in Innovation Initiative of the Society of Cardiovascular Angiography and Interventions.

Sources of Funding

No funding source was available for the gathering of these data, statistical analyses, or drafting of this report. The collaborative nature of the present investigation initiative has been reported previously.[6] All of the contacted principal investigators and device manufacturers shared individual patient data for female patients enrolled in randomized controlled trials evaluating the safety and efficacy of different types of DES.

Disclosures

Dr Stefanini received speaker fees from Abbott Vascular, AstraZeneca, Biosensors, and Biotronik. Dr Windecker has received research contracts to the institution from Abbott, Boston Scientific, Biosensors, Cordis, and Medtronic. Dr Wijns has received institutional research grants from Boston, Medtronic, Abbott, Terumo, Biosensors and is an investigator for sponsored trials by Boston, Medtronic, Abbott, Terumo, and Biosensors. Fees or honoraria on behalf of Dr Wijns from Boston, Medtronic, Abbott, Terumo, and Biosensors go to the Cardiovascular Center Aalst. Dr Von Birgelen is a consultant to and has received lecture fees or travel expenses from Abbott Vascular, Biotronik, Boston Scientific, Medtronic, and Merck Sharp and Dohme. Dr Von Birgelen's research department Thoraxcentrum Twente has received educational or research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. Dr Kandzari has received research or grant support from Medtronic, Abbott, and Boston Scientific and consulting honoraria from Medtronic and Boston Scientific. Dr Valgimigli has received honoraria for lectures or advisory board and research grants from

Merck, Iroko, Eli Lilly, and Medtronic; honoraria for advisory board and lectures from Medicines Company, Eli Lilly, Daiichi Sankyo, St Jude, and Abbott Vascular; and honoraria for lectures from Cordis, Carbostent and Implantable Devices, and Terumo. Dr Galatius has received grant support from St Jude, Abbot, Terumo, and Biotronik and advisory board honorarium from Eli Lilly and Servier. Dr Smits has received institutional research grants from Abbott Vascular, Boston Scientific, St. Jude, and Terumo. Dr Steg received research grants (to INSERM U1148) from Servier, Sanofi; served as a speaker or consultant for Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, BristolMyersSquibb, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Medtronic, Merck-Sharpe Dohme, Novartis, Orexigen, Pfizer, Regado, Sanofi, Servier, The Medicines Company; and is stockholder of Aterovax. Dr Kastrati reports having received honoraria from Abbott, Biosensors, Biotronik, Cordis, and Medtronic and a patent application in respect of a biodegradable polymer stent coating. Dr Stone has been a consultant for Abbott Vascular, Boston Scientific, Bristol-Myers Squibb–Sanofi partnership, Eli Lilly, Daiichi Sankyo, AstraZeneca, and The Medicines Company. Dr Dangas is consultant for GE HealthCare, Janssen Pharmaceuticals Inc, and Medtronic Inc; is in the scientific advisory board of AstraZeneca; and is stockholder of Claret Medical Inc and Elixir Medical Corporation. Dr Mehran has received institutional research grant support from the Medicines Company, Bristol-Myers Squibb and Sanofi -Aventis, Eli Lilly, and AstraZeneca and consulting fees from AstraZeneca, Bayer, CSL Behring, Janssen Pharmaceuticals inc, Merck & Co., Osprey Medical Inc, Watermark Research Partners and serves on the advisory board of Abbott Laboratories, Boston Scientific Corporation, Covidien, Janssen Pharmaceuticals, The Medicines Company, Sanofi-Aventis. The other authors have no conflicts of interest to disclose.

References

1. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol*. 2005;46:937–954. doi: 10.1016/j.jacc.2005.03.074.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29–e322. doi: 10.1161/CIR.0000000000000152.
3. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–1717. doi: 10.1056/NEJMoa060989.
4. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800. doi: 10.1056/NEJMoa1500857.
5. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, Fox KA, Lipka LJ, Liu X, Nicolau JC, Ophuis AJ, Paolasso E, Scirica BM, Spinar J, Theroux P, Wiviott SD, Strony J, Murphy SA; TRA 2P–TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med*. 2012;366:1404–1413. doi: 10.1056/NEJMoa1200933.
6. Stefanini GG, Baber U, Windecker S, Morice MC, Sartori S, Leon MB, Stone GW, Serruys PW, Wijns W, Weisz G, Camenzind E, Steg PG, Smits PC, Kandzari D, Von Birgelen C, Galatius S, Jeger RV, Kimura T, Mikhail GW, Itchhaporia D, Mehta L, Ortega R, Kim HS, Valgimigli M, Kastrati A, Chieffo A, Mehran R. Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomised trials. *Lancet*. 2013;382:1879–1888. doi: 10.1016/S0140-6736(13)61782-1.
7. Bittl JA. Percutaneous coronary interventions in the diabetic patient: where do we stand? *Circ Cardiovasc Interv*. 2015;8:e001944. doi: 10.1161/CIRCINTERVENTIONS.114.001944.
8. Bench TJ, Parikh PB, Jeremias A, Brener SJ, Naidu SS, Shlofmitz RA, Pappas T, Marzo KP, Gruberg L. The impact of previous revascularization on clinical outcomes in patients undergoing primary percutaneous coronary intervention. *J Invasive Cardiol*. 2013;25:166–169.
9. Wilson WM, Andrianopoulos N, Clark D, Duffy SJ, Brennan A, Harries I, New G, Sebastian M, Loane P, Reid C, Ajani AE. Long-term predictors of mortality after percutaneous coronary intervention in the era of drug-eluting stents. *Am J Cardiol*. 2011;108:936–942. doi: 10.1016/j.amjcard.2011.05.024.
10. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabatè M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet*. 2012;379:1393–1402. doi: 10.1016/S0140-6736(12)60324-9.
11. Stefanini GG, Serruys PW, Silber S, Khattab AA, van Geuns RJ, Richardt G, Buszman PE, Kelbæk H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, Di Mario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli AL, Gobbens P, Windecker S. The impact of patient and lesion complexity on clinical and angiographic outcomes after revascularization with zotarolimus- and everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial (a randomized comparison of a zotarolimus-eluting stent with an everolimus-eluting stent for percutaneous coronary intervention). *J Am Coll Cardiol*. 2011;57:2221–2232. doi: 10.1016/j.jacc.2011.01.036.
12. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (caprie). Caprie steering committee. *Lancet*. 1996;348:1329–1339.
13. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Fabry-Ribaudo L, Hu T, Topol EJ, Fox KA; CHARISMA Investigators. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol*. 2007;49:1982–1988. doi: 10.1016/j.jacc.2007.03.025.
14. Giustino G, Baber U, Stefanini GG, Aquino M, Stone GW, Sartori S, Steg PG, Wijns W, Smits PC, Jeger RV, Leon MB, Windecker S, Serruys PW, Morice MC, Camenzind E, Weisz G, Kandzari D, Dangas GD, Mastoris I, Von Birgelen C, Galatius S, Kimura T, Mikhail G, Itchhaporia D, Mehta L, Ortega R, Kim HS, Valgimigli M, Kastrati A, Chieffo A, Mehran R. Impact of clinical presentation (stable angina pectoris vs unstable angina pectoris or non-ST-elevation myocardial infarction vs ST-elevation myocardial infarction) on long-term outcomes in women undergoing percutaneous coronary intervention with drug-eluting stents. *Am J Cardiol*. 2015;116:845–852. doi: 10.1016/j.amjcard.2015.06.010.
15. Kirtane AJ, Kelly CR. Clearing the air on the "smoker's paradox". *J Am Coll Cardiol*. 2015;65:1116–1118. doi: 10.1016/j.jacc.2015.01.012.
16. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC Jr, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1999;100:1134–1146.
17. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, Sharma SK, Pocock SJ, Dangas GD. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2015;65:1298–1310. doi: 10.1016/j.jacc.2015.01.039.
18. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, Abizaid A, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Genereux P, Bhatt DL, Orlandi C, De Servi S, Petrou M, Rapezzi C, Stone GW. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. *Lancet*. 2015;385:2371–2382. doi: 10.1016/S0140-6736(15)60263-X.
19. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226–235. doi: 10.1056/NEJMoa1002358.

Circulation
Cardiovascular Interventions

Safety and Efficacy of New-Generation Drug-Eluting Stents in Women at High Risk for Atherothrombosis: From the Women in Innovation and Drug-Eluting Stents Collaborative Patient-Level Pooled Analysis

Gennaro Giustino, Usman Baber, Olga Salianski, Samantha Sartori, Gregg W. Stone, Martin B. Leon, Melissa Aquino, Giulio G. Stefanini, P. Gabriel Steg, Stephan Windecker, Monica O' Donoghue, William Wijns, Patrick W. Serruys, Marco Valgimigli, Marie-Claude Morice, Edoardo Camenzind, Giora Weisz, Pieter C. Smits, David Kandzari, Clemens Von Birgelen, George D. Dangas, Jin Y. Cha, Soren Galatius, Raban V. Jeger, Takeshi Kimura, Ghada W. Mikhail, Dipti Itchhaporia, Laxmi Mehta, Rebecca Ortega, Hyo-Soo Kim, Adnan Kastrati, Philippe Genereux, Alaide Chieffo and Roxana Mehran

Circ Cardiovasc Interv. 2016;9:e002995
doi: 10.1161/CIRCINTERVENTIONS.115.002995
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7640. Online ISSN: 1941-7632

APPENDIX

Supplementary Tables

Supplementary Table 1. Characteristics of included randomized controlled trials. CAD: Coronary Artery Disease; BMS: Bare Metal Stent; NSTEMI: Non-ST segment Elevation Myocardial Infarction; STEMI: ST segment Elevation Myocardial Infarction; UA: Unstable Angina. Cypher and Cordis, Johnson & Johnson, Miami Lakes, FL, USA; Taxus, Boston Scientific, Natick, MA, USA; Xience, Abbott Vascular, Santa Clara, CA, USA; Promus, Boston Scientific; Endeavor, Medtronic, Santa Rosa, CA, USA; Resolute, Medtronic; Biomatrix, Biosensors, Newport Beach, CA, USA; Nobori, Terumo, Tokyo, Japan; Yukon, Translumina, Hechingen, Germany.

Study	Year	Patients	Women	Stents used	Key inclusion criteria	Key exclusion criteria
RAVEL[1]	2002	238	58 (24)	Cypher, BMS	Stable CAD or UA, single de-novo lesion	NSTEMI or STEMI
SIRIUS[2]	2003	1058	305 (29%)	Cypher, BMS	Stable CAD or UA, single de-novo lesion	NSTEMI or STEMI
E-SIRIUS[3]	2003	352	103 (29%)	Cypher, BMS	Stable CAD or UA, single de-novo lesion	NSTEMI or STEMI
C-SIRIUS[4]	2004	100	31 (31%)	Cypher, BMS	Stable CAD or UA, single de-novo lesion	NSTEMI or STEMI
TAXUS I[5]	2003	61	7 (11%)	Taxus, BMS	Stable CAD or UA, single lesion	NSTEMI or STEMI
TAXUS II SR[6]	2003	267	67 (25%)	Taxus, BMS	Stable CAD or UA, single de-	NSTEMI or STEMI

					novo lesion	
TAXUS IV[7]	2004	1314	367 (28%)	Taxus, BMS	Stable CAD or UA, single de-novo lesion	NSTEMI or STEMI
TAXUS V[8]	2005	1156	353 (31%)	Taxus, BMS	Stable CAD or UA, single de-novo lesion	NSTEMI or STEMI
SIRTAX[9]	2005	1012	231 (23%)	Cypher, Taxus	Stable CAD or UA, single de-novo lesion	None
ENDEAVOR II[10]	2006	1197	283 (24%)	Endeavor, BMS	Stable CAD or UA, single de-novo lesion	NSTEMI or STEMI
ENDEAVOR III[11]	2006	436	133 (31%)	Endeavor, Cypher	Stable CAD or UA, single de-novo lesion	NSTEMI or STEMI
ENDEAVOR IV[12]	2010	1548	500 (32%)	Endeavor, Taxus	Stable CAD or UA, single de-novo lesion	NSTEMI or STEMI
PROTECT[13]	2012	8709	2061 (24%)	Endeavor, Cypher	Stable CAD or UA, single de-novo lesion	None
RESOLUTE AC[14]	2010	2292	529 (23%)	Resolute, Xience	Stable CAD, UA, NSTEMI or STEMI	None
TWENTE[15]	2012	1391	382 (27%)	Resolute, Xience	Stable CAD, UA or NSTEMI	STEMI
SPIRIT II[16]	2006	300	80 (27%)	Xience, Taxus	Stable CAD, UA or 2 de-novo lesions	NSTEMI or STEMI
SPIRIT III[17]	2008	1002	314 (31)	Xience, Taxus	Stable CAD, UA or 2 de-novo lesions	NSTEMI or STEMI

SPIRIT IV[18]	2010	3687	1189 (32)	Xience, Taxus	Stable CAD, UA or 3 de-novo lesions	NSTEMI or STEMI
COMPARE I[19]	2010	1800	526 (29%)	Xience, Taxus	Stable CAD, UA, NSTEMI or STEMI	None
BASKET-PROVE[20]	2010	2314	565 (24%)	Xience, Cypher, BMS	Stable CAD, UA or acute MI, target vessel diameter ≥ 3.0 mm	None
EXCELLENT[21]	2011	1443	512 (35%)	Xience, Promus, Cypher	Stable CAD, UA, NSTEMI	STEMI
RESET[22]	2012	3197	742 (23%)	Xience, Cypher	Stable CAD, UA, NSTEMI or STEMI	None
PRODIGY[23]	2012	2013	473 (23%)	Xience, Promus, Endeavor, Taxus, BMS	Stable CAD, UA, NSTEMI or STEMI	None
LEADERS[24]	2008	1707	430 (25%)	Biomatrix, Cypher	Stable CAD, UA, NSTEMI or STEMI	None
COMPARE II[25]	2013	2707	293 (26%)	Nobori, Xience, Promus	Stable CAD, UA, NSTEMI or STEMI	None
ISAR-TEST 4[26]	2009	2603	623 (24%)	Yukon, Xience, Cypher	Stable CAD, UA, NSTEMI or STEMI	None

Supplementary Table 2. Clinical endpoint definitions used across randomized controlled trials. ARC: Academic Research Consortium; CK: Creatine-Kinase; ECG = Electrocardiogram; MI: Myocardial Infarction; URL: Upper Reference Limit.

Trial name	Myocardial infarction	Target lesion revascularization	Stent thrombosis
RAVEL	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent.	ARC criteria
SIRIUS	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent.	ARC criteria
E-SIRIUS	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent.	ARC criteria
C-SIRIUS	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent.	ARC criteria

TAXUS I	Development of Q waves in ≥2 contiguous leads with CK and CK-MB levels elevated above normal	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent.	ARC criteria
TAXUS II SR	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent.	ARC criteria
TAXUS IV	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent.	ARC criteria
TAXUS V	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
SIRTAX	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB or troponin I	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
ENDEAVOR II	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK level	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the	ARC criteria

	≥2*ULN and increased level of CK-MB	stent or within the 5-mm borders proximal or distal to the stent	
ENDEAVOR III	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
ENDEAVOR IV	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
			ARC criteria
PROTECT	II Universal Definition (Thygesen K et al. Circulation 2007): Periprocedural MI: cardiac biomarkers increase ≥3*ULN Spontaneous: Typical rise and fall of cardiac biomarkers (preferably troponin) with at least 1 value >URL and at least 1 of the following: symptoms, ST-T changes at ECG, pathological Q waves, or imaging evidence of ischemia	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
RESOLUTE AC	Extended historical definition (Vranckx et al. Eurointervention 2010). In summary: development of Q waves in ≥2 contiguous leads and elevated cardiac enzymes or, in the absence of Q waves, increase in the	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria

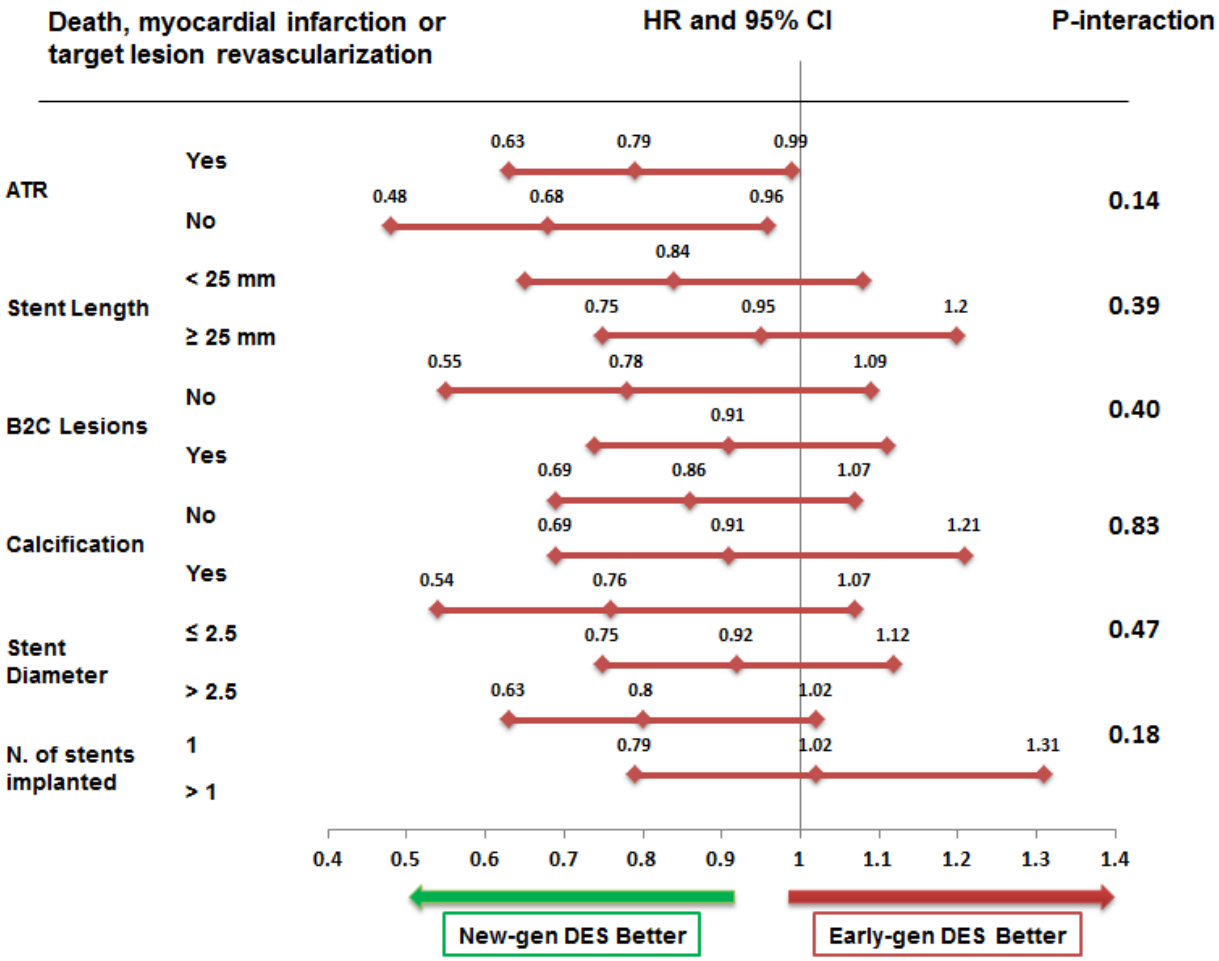
	CK level ≥2*ULN and increased level of CK-MB or troponin. In patients with acute MI at baseline: if cardiac biomarkers still raising new chest pain of ischemia equivalent and rise in cardiac biomarkers >50% previous level; if cardiac biomarkers have returned to normal, CK level ≥2*ULN.		
TWENTE	Extended historical definition (Vranckx et al. Eurointervention 2010). In summary: development of Q waves in ≥2 contiguous leads and elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB or troponin. In patients with acute MI at baseline: if cardiac biomarkers still raising new chest pain of ischemia equivalent and rise in cardiac biomarkers >50% previous level; if cardiac biomarkers have returned to normal, CK level ≥2*ULN.	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
SPIRIT II	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, a typical rise and fall of CK-MB (if non-procedural/spontaneous MI, CK-MB >2 times upper limit of normal; if post PCI, CK-MB >3 times upper limit of normal; if post CABG, CK-MB >5 times upper limit of normal)	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria

SPIRIT III	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
SPIRIT IV	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
COMPARE	Periprocedural MI (in patients without acute MI at baseline): any elevation in concentrations of CK ≥2*ULN and increase in CK-MB or troponin. Spontaneous MI: typical rise and fall of troponin or CK-MB with at least one of the following: ischemic symptoms, development of pathological Q waves, ischemic ECG changes, or pathological findings of an acute MI	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
BASKET-PROVE	Typical rise and fall of cardiac biomarkers (preferably troponin) with at least 1 value >URL and at least 1 of the following: symptoms, ST-T changes at ECG, pathological Q waves, or recent angioplasty.	Target vessel Revascularization was used	ARC criteria
EXCELLENT	Academic Research Consortium criteria (Cutlip DE et al. Circulation 2007) In summary:	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the	ARC criteria

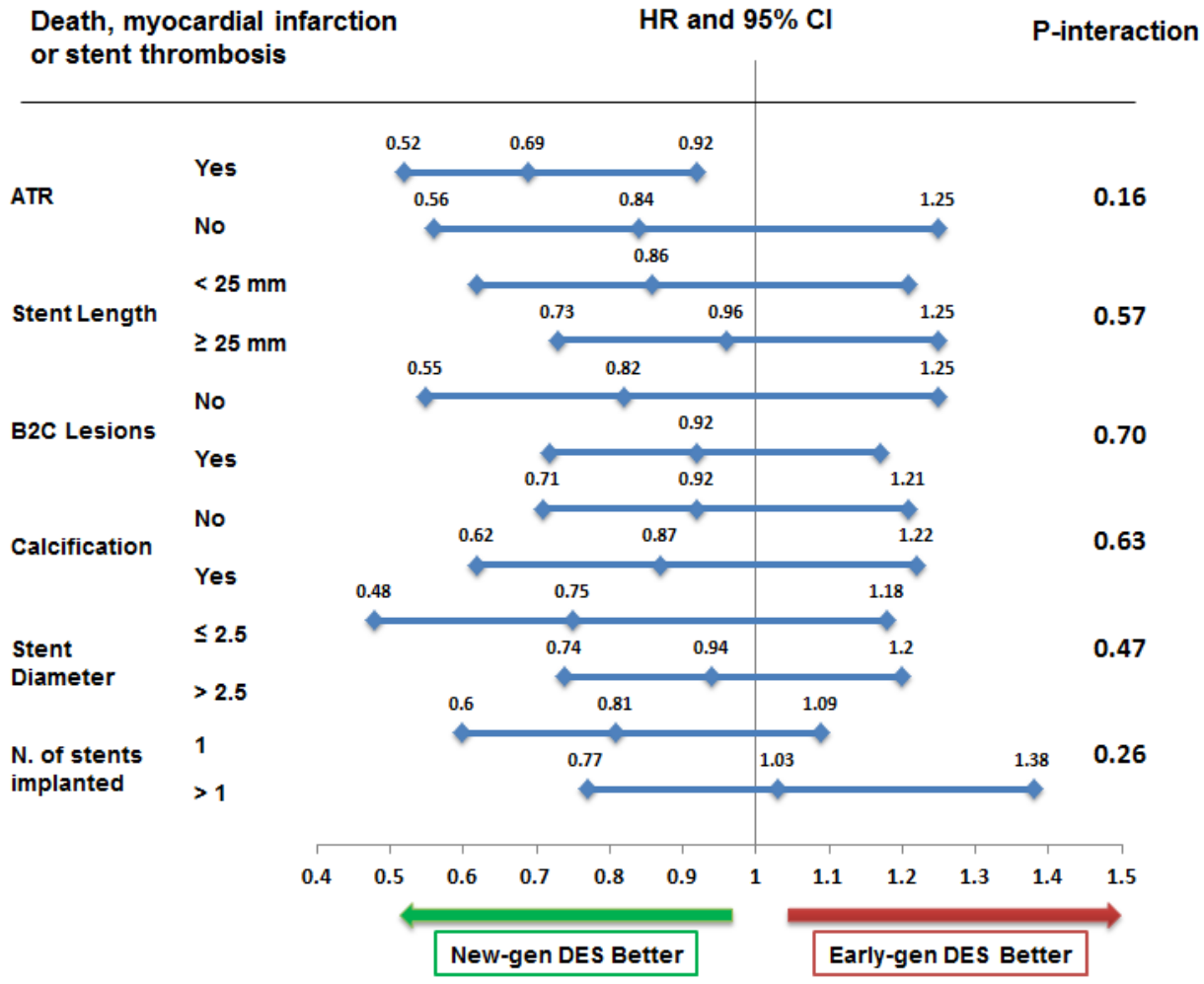
	Periprocedural MI: troponin >3*URL or CK-MB>3*URL if baseline cardiac biomarkers <URL. Stable or decreasing values on 2 samples followed by 20% increase if baseline cardiac biomarkers >URL. Spontaneous MI: troponin >URL or CK-MB >URL	stent or within the 5-mm borders proximal or distal to the stent	
RESET	Periprocedural MI: CK-MB ≥3*ULN or CK ≥3*ULN in the absence of CKMB measurement. Spontaneous MI: Academic Research Consortium criteria (Cutlip DE et al. Circulation 2007), troponin >URL or CK-MB >URL	Revascularisation for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
			ARC criteria
PRODIGY	II Universal Definition (Thygesen K et al. Circulation 2007): Periprocedural MI: cardiac biomarkers increase ≥3*ULN Spontaneous: Typical rise and fall of cardiac biomarkers (preferably troponin) with at least 1 value >URL and at least 1 of the following: symptoms, ST-T changes at ECG, pathological Q waves, or imaging evidence of ischemia	Target vessel Revascularisation was used	ARC criteria
LEADERS	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK level ≥2*ULN and increased level of CK-MB or troponin I	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria

COMPARE-2	Periprocedural MI (in patients without acute MI at baseline):any elevation in concentrations of CK ≥2*ULN and increase in CK-MB or troponin. Spontaneous MI: typical rise and fall of troponin or CK-MB with at least one of the following: ischemic symptoms, development of pathological Q waves, ischemic ECG changes, or pathological findings of an acute MI	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria
ISAR-TEST 4	Periprocedural MI: CK-MB (or CK) ≥3*ULN and at least 50% over the most recent pre-PCI levels, or the development of new ECG changes consistent with MI and CK-MB (CK) elevation >ULN at 2 measurements for patients with stable angina pectoris or NSTE-ACS and falling or normal CK-MB (CK) levels. Recurrent chest pain lasting .30 min with either new ECG changes consistent with second MI or next CK-MB (CK) level at least 8–12 h after PCI elevated at least 50% above the previous level was considered procedure-related MI for patients presenting with elevated CK-MB (CK) level prior to PCI. Spontaneous MI: any CK-MB increase with or without the development of Q-waves on ECG.	Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	ARC criteria

Supplementary Figure 1. Risk of death, myocardial infarction or target lesion revascularization with early- versus new-generation drug-eluting stents across anatomical and procedural subgroups.



Supplementary Figure 2. Risk of death, myocardial infarction or stent thrombosis with early- versus new-generation drug-eluting stents across anatomical and procedural subgroups.



Supplementary References

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.

2. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315-23.

3. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362:1093-9.

4. Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, Kuntz RE, Popma JJ. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol 2004;43:1110-5.

5. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, Russell ME. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107:38-42.

6. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108:788-94.

7. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221-31.

8. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, O'Shaughnessy CD, DeMaio S, Hall P, Popma JJ, Koglin J, Russell ME. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. Jama 2005;294:1215-23.

9. Windecker S, Remondino A, Eberli FR, Juni P, Raber L, Wenaweser P, Togni M, Billinger M, Tuller D, Seiler C, Roffi M, Corti R, Sutsch G, Maier W, Luscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653-62.
10. Fajadet J, Wijns W, Laarman GJ, Kuck KH, Ormiston J, Munzel T, Popma JJ, Fitzgerald PJ, Bonan R, Kuntz RE. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. Circulation 2006;114:798-806.
11. Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW, Turco M, Applegate RJ, Gurbel PA, Midei MG, Badre SS, Mauri L, Thompson KP, LeNarz LA, Kuntz RE. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol 2006;48:2440-7.
12. Leon MB, Mauri L, Popma JJ, Cutlip DE, Nikolsky E, O'Shaughnessy C, Overlie PA, McLaurin BT, Solomon SL, Douglas JS, Jr., Ball MW, Caputo RP, Jain A, Tolleson TR, Reen BM, 3rd, Kirtane AJ, Fitzgerald PJ, Thompson K, Kandzari DE. A randomized comparison of the Endeavor zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions 12-month outcomes from the ENDEAVOR IV trial. J Am Coll Cardiol 2010;55:543-54.
13. Camenzind E, Wijns W, Mauri L, Kurowski V, Parikh K, Gao R, Bode C, Greenwood JP, Boersma E, Vranckx P, McFadden E, Serruys PW, O'Neil WW, Jorissen B, Van Leeuwen F, Steg PG. Stent thrombosis and major clinical events at 3 years after zotarolimus-eluting or sirolimus-eluting coronary stent implantation: a randomised, multicentre, open-label, controlled trial. Lancet 2012;380:1396-405.
14. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136-46.
15. von Birgelen C, Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JH, Linssen GC, Said SA, Kleijne MA, Sen H, Lowik MM, van der Palen J,

Verhorst PM, de Man FH. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol 2012;59:1350-61.

16. Serruys PW, Ruygrok P, Neuzner J, Piek JJ, Seth A, Schofer JJ, Richardt G, Wiemer M, Carrie D, Thuesen L, Boone E, Miquel-Herbert K, Daemen J. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent:the SPIRIT II trial. EuroIntervention 2006;2:286-94.

17. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Mahaffey KW, Cutlip DE, Fitzgerald PJ, Sood P, Su X, Lansky AJ. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. Jama 2008;299:1903-13.

18. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663-74.

19. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201-9.

20. Kaiser C, Galatius S, Erne P, Eberli F, Alber H, Rickli H, Pedrazzini G, Hornig B, Bertel O, Bonetti P, De Servi S, Brunner-La Rocca HP, Ricard I, Pfisterer M. Drug-eluting versus bare-metal stents in large coronary arteries. N Engl J Med 2010;363:2310-9.

21. Park KW, Chae IH, Lim DS, Han KR, Yang HM, Lee HY, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Jo SH, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Gwon HC, Jang YS, Kim HS. Everolimus-eluting versus sirolimus-eluting stents in patients undergoing percutaneous coronary intervention: the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) randomized trial. J Am Coll Cardiol 2011;58:1844-54.

22. Kimura T, Morimoto T, Natsuaki M, Shiomi H, Igarashi K, Kadota K, Tanabe K, Morino Y, Akasaka T, Takatsu Y, Nishikawa H, Yamamoto Y, Nakagawa Y, Hayashi Y, Iwabuchi M, Umeda H, Kawai K, Okada H, Kimura K, Simonton CA, Kozuma K. Comparison of everolimus-eluting and sirolimus-eluting coronary stents: 1-year outcomes from the Randomized Evaluation

of Sirolimus-eluting Versus Everolimus-eluting stent Trial (RESET). Circulation 2012;126:1225-36.

23. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fuca G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012;125:2015-26.

24. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163-73.

25. Smits PC, Hofma S, Togni M, Vazquez N, Valdes M, Voudris V, Slagboom T, Goy JJ, Vuillomenet A, Serra A, Nouche RT, den Heijer P, van der Ent M. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. Lancet 2013;381:651-60.

26. Byrne RA, Kastrati A, Kufner S, Massberg S, Birkmeier KA, Laugwitz KL, Schulz S, Pache J, Fusaro M, Seyfarth M, Schomig A, Mehilli J. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial. Eur Heart J 2009;30:2441-9.