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 Saliantski; 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 Weiss, 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 10449 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 (Pinteraction =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 Ì high atherothrombotic risk Ì myocardial infarction Ì percutaneous coronary intervention Ì women

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From 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.M.); Department of Cardiology, Hoag Memorial Hospital Presbyterian, Newport Beach, CA (D.K.); Department of Cardiology, Thoraxcentrum Twente, Enschede, Netherlands (C.V.B.); 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-Vrouwenziekenhuis Ziekenhuis, Aalst, Belgium (W.W.); Department 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.K.); 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, Herzcentrum, 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.G.).

The Data Supplement is available at http://circinterventions.ahajournals.orglookup/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@moun.tsinai.org

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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 anti-thrombotic 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 thrombosis.
- 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. 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. Importantly, about 488,000 of these patients were women. Women also constitute about one third of all patients treated with percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation. 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 database, list of trials, analytic strategies, and prespecified end points has been previously reported. 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).
in the Data Supplement). Characteristics of the RCTs included in the present study are summarized in the Table 1 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) study 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.

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 (Cypher and 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), bio-limus-eluting stents with biodegradable polymer coating (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. Failures 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- versus late-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.

**Results**

**Baseline Characteristics**

Out of 10,449 women included in the pooled database, 5,333 (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
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: 0.30–0.88), 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,
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. 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. Although studies, such as the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE), a substudy from CHARISMA in high-risk patients, and others, 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. 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. 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

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

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.
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. 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, the nature of the crude relationship between PR and PMI with adverse outcomes is most likely correlational 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.

**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.

**Figure 5.** Kaplan–Meier curves for the composite of all-cause mortality, myocardial infarction (MI), or 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.2,18; (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 (anti-ischemic) 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 vascularity. 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
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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.4 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, Merck Sharp and Dohme. Dr Von Birgelen’s research department Thoraxcentrum Twente has received educational or research grants 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...
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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


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## 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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Women</th>
<th>Stents used</th>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL¹</td>
<td>2002</td>
<td>238</td>
<td>58 (24)</td>
<td>Cypher, BMS</td>
<td>Stable CAD or UA, single de-novo lesion</td>
<td>NSTEMI or STEMI</td>
</tr>
<tr>
<td>SIRIUS²</td>
<td>2003</td>
<td>1058</td>
<td>305 (29%)</td>
<td>Cypher, BMS</td>
<td>Stable CAD or UA, single de-novo lesion</td>
<td>NSTEMI or STEMI</td>
</tr>
<tr>
<td>E-SIRIUS³</td>
<td>2003</td>
<td>352</td>
<td>103 (29%)</td>
<td>Cypher, BMS</td>
<td>Stable CAD or UA, single de-novo lesion</td>
<td>NSTEMI or STEMI</td>
</tr>
<tr>
<td>C-SIRIUS⁴</td>
<td>2004</td>
<td>100</td>
<td>31 (31%)</td>
<td>Cypher, BMS</td>
<td>Stable CAD or UA, single de-novo lesion</td>
<td>NSTEMI or STEMI</td>
</tr>
<tr>
<td>TAXUS I⁵</td>
<td>2003</td>
<td>61</td>
<td>7 (11%)</td>
<td>Taxus, BMS</td>
<td>Stable CAD or UA, single lesion</td>
<td>NSTEMI or STEMI</td>
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<tr>
<td>TAXUS II SR⁶</td>
<td>2003</td>
<td>267</td>
<td>67 (25%)</td>
<td>Taxus, BMS</td>
<td>Stable CAD or UA, single de-novo lesion</td>
<td>NSTEMI or STEMI</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Participants</td>
<td>Lesions (%)</td>
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<td>Lesion Type</td>
<td></td>
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</tr>
<tr>
<td>TAXUS IV</td>
<td>2004</td>
<td>1314</td>
<td>367 (28%)</td>
<td>Taxus, BMS</td>
<td>Stable CAD or UA, single de-novo lesion</td>
<td></td>
</tr>
<tr>
<td>TAXUS V</td>
<td>2005</td>
<td>1156</td>
<td>353 (31%)</td>
<td>Taxus, BMS</td>
<td>Stable CAD or UA, single de-novo lesion</td>
<td></td>
</tr>
<tr>
<td>SIRTAX</td>
<td>2005</td>
<td>1012</td>
<td>231 (23%)</td>
<td>Cypher, Taxus</td>
<td>Stable CAD or UA, single de-novo lesion</td>
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<tr>
<td>ENDEAVOR II</td>
<td>2006</td>
<td>1197</td>
<td>283 (24%)</td>
<td>Endeavor, BMS</td>
<td>Stable CAD or UA, single de-novo lesion</td>
<td></td>
</tr>
<tr>
<td>ENDEAVOR III</td>
<td>2006</td>
<td>436</td>
<td>133 (31%)</td>
<td>Endeavor, Cypher</td>
<td>Stable CAD or UA, single de-novo lesion</td>
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<tr>
<td>ENDEAVOR IV</td>
<td>2010</td>
<td>1548</td>
<td>500 (32%)</td>
<td>Endeavor, Taxus</td>
<td>Stable CAD or UA, single de-novo lesion</td>
<td></td>
</tr>
<tr>
<td>PROTECT</td>
<td>2012</td>
<td>8709</td>
<td>2061 (24%)</td>
<td>Endeavor, Cypher</td>
<td>Stable CAD or UA, single de-novo lesion</td>
<td></td>
</tr>
<tr>
<td>RESOLUTE AC</td>
<td>2010</td>
<td>2292</td>
<td>529 (23%)</td>
<td>Resolute, Xience</td>
<td>Stable CAD, UA, NSTEMI or STEMI</td>
<td></td>
</tr>
<tr>
<td>TWENTE</td>
<td>2012</td>
<td>1391</td>
<td>382 (27%)</td>
<td>Resolute, Xience</td>
<td>Stable CAD, UA or NSTEMI or STEMI</td>
<td></td>
</tr>
<tr>
<td>SPIRIT II</td>
<td>2006</td>
<td>300</td>
<td>80 (27%)</td>
<td>Xience, Taxus</td>
<td>Stable CAD, UA or 2 de-novo lesions</td>
<td></td>
</tr>
<tr>
<td>SPIRIT III</td>
<td>2008</td>
<td>1002</td>
<td>314 (31%)</td>
<td>Xience, Taxus</td>
<td>Stable CAD, UA or 2 de-novo lesions</td>
<td></td>
</tr>
<tr>
<td>Trial</td>
<td>Year</td>
<td>Patients</td>
<td>Patients (%)</td>
<td>Stents Used</td>
<td>Lesion Type</td>
<td>Event Type</td>
</tr>
<tr>
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<td>--------------------------</td>
</tr>
<tr>
<td>SPIRIT IV</td>
<td>2010</td>
<td>3687</td>
<td>1189 (32%)</td>
<td>Xience, Taxus</td>
<td>Stable CAD, UA or 3 de-novo lesions</td>
<td>NSTEMI or STEMI</td>
</tr>
<tr>
<td>COMPARE I</td>
<td>2010</td>
<td>1800</td>
<td>526 (29%)</td>
<td>Xience, Taxus</td>
<td>Stable CAD, UA, NSTEMI or STEMI</td>
<td>None</td>
</tr>
<tr>
<td>BASKET-PROVE</td>
<td>2010</td>
<td>2314</td>
<td>565 (24%)</td>
<td>Xience, Cypher, BMS</td>
<td>Stable CAD, UA or acute MI,</td>
<td>None</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>2011</td>
<td>1443</td>
<td>512 (35%)</td>
<td>Xience, Promus, Cypher</td>
<td>Stable CAD, UA, NSTEMI</td>
<td>STEMI</td>
</tr>
<tr>
<td>RESET</td>
<td>2012</td>
<td>3197</td>
<td>742 (23%)</td>
<td>Xience, Cypher</td>
<td>Stable CAD, UA, NSTEMI or STEMI</td>
<td>None</td>
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<tr>
<td>PRODIGY</td>
<td>2012</td>
<td>2013</td>
<td>473 (23%)</td>
<td>Xience, Promus, Endeavor, Taxus, BMS</td>
<td>Stable CAD, UA, NSTEMI or STEMI</td>
<td>None</td>
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<tr>
<td>LEADERS</td>
<td>2008</td>
<td>1707</td>
<td>430 (25%)</td>
<td>Biomatrix, Cypher</td>
<td>Stable CAD, UA, NSTEMI or STEMI</td>
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</tr>
<tr>
<td>COMPARE II</td>
<td>2013</td>
<td>2707</td>
<td>293 (26%)</td>
<td>Nobori, Xience, Promus</td>
<td>Stable CAD, UA, NSTEMI or STEMI</td>
<td>None</td>
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<tr>
<td>ISAR-TEST 4</td>
<td>2009</td>
<td>2603</td>
<td>623 (24%)</td>
<td>Yukon, Xience, Cypher</td>
<td>Stable CAD, UA, NSTEMI or STEMI</td>
<td>None</td>
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</table>
### 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.

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Myocardial infarction</th>
<th>Target lesion revascularization</th>
<th>Stent thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL</td>
<td>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</td>
<td>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.</td>
<td>ARC criteria</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>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</td>
<td>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.</td>
<td>ARC criteria</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>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</td>
<td>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.</td>
<td>ARC criteria</td>
</tr>
<tr>
<td>C-SIRIUS</td>
<td>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</td>
<td>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.</td>
<td>ARC criteria</td>
</tr>
<tr>
<td>Study</td>
<td>Criteria</td>
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<td>ARC criteria</td>
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<tr>
<td>----------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>TAXUS I</td>
<td>Development of Q waves in ≥2 contiguous leads with CK and CK-MB levels elevated above normal</td>
<td>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.</td>
<td>ARC criteria</td>
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<tr>
<td>TAXUS II SR</td>
<td>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</td>
<td>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.</td>
<td>ARC criteria</td>
</tr>
<tr>
<td>TAXUS IV</td>
<td>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</td>
<td>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.</td>
<td>ARC criteria</td>
</tr>
<tr>
<td>TAXUS V</td>
<td>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</td>
<td>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</td>
<td>ARC criteria</td>
</tr>
<tr>
<td>SIRTAX</td>
<td>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</td>
<td>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</td>
<td>ARC criteria</td>
</tr>
<tr>
<td>ENDEAVOR II</td>
<td>Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK level</td>
<td>Revascularization for ischemia for a stenosis of the luminal diameter anywhere within the</td>
<td>ARC criteria</td>
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<tr>
<td>Study</td>
<td>Criteria</td>
<td>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</td>
<td></td>
</tr>
<tr>
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<td>--------------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>ENDEAVOR III</td>
<td>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</td>
<td>ARC criteria</td>
<td></td>
</tr>
<tr>
<td>ENDEAVOR IV</td>
<td>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</td>
<td>ARC criteria</td>
<td></td>
</tr>
<tr>
<td>PROTECT II</td>
<td>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 &gt;URL and at least 1 of the following: symptoms, ST-T changes at ECG, pathological Q waves, or imaging evidence of ischemia</td>
<td>ARC criteria</td>
<td></td>
</tr>
<tr>
<td>RESOLUTE AC</td>
<td>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</td>
<td>ARC criteria</td>
<td></td>
</tr>
</tbody>
</table>
CK level $\geq 2^{*}\text{ULN}$ 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 $\geq 2^{*}\text{ULN}$.

**TWENTE** Extended historical definition (Vranckx et al. Eurointervention 2010). In summary: development of Q waves in $\geq 2$ contiguous leads and elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level $\geq 2^{*}\text{ULN}$ 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 $\geq 2^{*}\text{ULN}$.

**SPIRIT II** Development of Q waves in $\geq 2$ 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

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

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

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

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

Target vessel Revascularisation was used

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

ARC criteria
<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of MI</th>
<th>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</th>
<th>ARC criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPARE-2</td>
<td>Periprocedural MI (in patients without acute MI at baseline): any elevation in concentrations of CK $\geq 2$*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</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>ISAR-TEST 4</td>
<td>Periprocedural MI: CK-MB (or CK) $\geq 3$*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 $&gt;ULN$ 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.</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>
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


对比在药物洗脱支架时代经 12 个月双抗治疗后的氯吡格雷与阿司匹林单药抗血小板疗效

几乎所有医生都要求接受了药物洗脱支架 (drug-eluting stents, DES) 植入术的患者使用阿司匹林加 P2Y 受体抑制剂双药联合抗血小板治疗 (dual-antiplatelet therapy, DAPT)，来防止术后血栓的再形成。尽管使用 12 个月以上的 DAPT 确实可以降低缺血性事件发生的风险，但同时也会增加出血性事件的风险。

在 DES 出现之前，有学者研究比较过单独使用阿司匹林或氯吡格雷对患者缺血性事件发生风险的影响，当时，阿司匹林显示出了压倒性的胜利。然而在 DES 出现后，还没有研究比较过 DES 植入后单用阿司匹林和单用氯吡格雷的效果，本次观察性研究就是要评价在 DES 植入后常规接受为期 12 个月的 DAPT 后再单用氯吡格雷或阿司匹林的临床效果和使用安全性。

本研究选取了 2003 年 1 月至 2010 年 12 月间行 DES 植入术后接受了为期 12 个月 DAPT，且未出现死亡、心肌梗死、卒中等不良临床反应的 3243 例患者，按照后续治疗方式将所有患者分为两组，阿司匹林组 (2472 例) 和氯吡格雷组 (771 例)，比较两组患者临床效果、血管造影和手术等特征后发现，相比于阿司匹林组，氯吡格雷组患者发生并发症和复杂病变的可能性更大。接受抗血小板单药治疗 36 个月后，氯吡格雷组患者并发心源性死亡、心肌梗死或卒中的风险较阿司匹林组低 (2.6% vs. 3.8%，HR = 0.54；95% CI 0.32-0.92；p = 0.02)，单独发生心源性死亡的风险也较低 (0.5% vs. 1.4%，HR = 0.31；95% CI 0.11-0.93；p = 0.04)。心肌梗死后溶栓治疗出血的风险两组相当 (1.3% vs. 0.9%，HR = 1.03；95% CI 0.46-2.32；p = 0.95)。

综上所述，对于 DES 植入术后接受 12 个月 DAPT 治疗无严重心脑血管并发症的患者，相较于单独使用阿司匹林，使用氯吡格雷单药治疗可更好地降低再发缺血性事件的风险，而两者发生出血性事件的风险相似。虽然本研究仍存在回顾性、分析性研究的局限性，但可以为术后患者使用单药抗血小板治疗提供一个新的选择。


新一代药物洗脱支架在具有动脉粥样硬化血栓形成高风险的女性患者中的安全性与疗效

动脉粥样硬化血栓形成是一种威胁生命安全的疾病，高风险的斑块破裂会导致血栓形成和动脉栓塞，从而导致外周缺血、卒中或急性冠脉综合征等症状。目前在全球范围内，冠状动脉、脑动脉及外周动脉系统的动脉粥样硬化性疾病是导致人类死亡的主要因素。根据美国心脏协会的数据，2010 年有 110 万美国群众发生了急性冠脉综合征，其中 48.8 万为女性。然而，与女性相关的研究数据却少之又少。
为探究新一代药物洗脱支架 (drug-eluting stents, DES) 对伴有多种动脉粥样硬化继发血栓形成风险 (atherothrombotic risk, ATR) 因素的女性患者的安全性与疗效，研究者汇集了来自 26 个随机试验中的 10449 例女性患者进行研究，并根据患者是否存在糖尿病史、经皮或外科冠状动脉重建史、心肌梗死史等高 ATR 因素将患者分为高 ATR 组 (5333 例，51%) 以及非高 ATR 组。主要研究终点为患者的心血管不良事件，包括全因死亡、心肌梗死或在 3 年内发生血管重建。

研究结果表明，高 ATR 组患者主要心血管不良事件发生率以及全因死亡率显著高于非高 ATR 组 (15.8% vs. 10.6%; 校正 HR = 1.53; 95% CI 1.34-1.75; p = 0.006)。与早期 DES 相比，应用新一代 DES 的高 ATR 组患者 3 年内主要心血管不良事件发生率显著降低 (校正 HR = 0.69; 95% CI 0.52-0.92)。在高 ATR 组和非高 ATR 组，患者使用新一代 DES 后主要心血管不良事件的获益一致，没有干扰证据 (Pinteraction = 0.14)。界标分析显示，高 ATR 组女性使用不同 DES 支架植入后 1 年内支架内血栓形成率为无显著差异，1~3 年内新一代 DES 支架内血栓形成发生率更低。

综上所述，高 ATR 患者使用新一代 DES 可明显获益，在 3 年随访期，新一代 DES 对于非常晚期血栓形成仍有实质性获益。


现有的阿司匹林过敏患者接受经皮冠状动脉介入治疗的用药安全及有效性
一项调查与系统评价

阿司匹林在急性冠脉综合征的治疗中发挥里重要的作用，可显著降低接受经皮冠状动脉介入 (percutaneous coronary intervention, PCI) 治疗患者的冠脉事件再发率，并对支架内血栓形成具有保护性作用。然而，有一些特殊的患者对阿司匹林过敏，在使用阿司匹林后会出现相关的不良反应，如呼吸道疾病恶化、荨麻疹、血管性水肿或过敏反应，这些都是具有停药指针的高危因素，有限的替代用药方案和鲜少的治疗经验，使得临床医生在管理这类患者时困难重重。

为了评估 PCI 患者合并阿司匹林过敏的最佳应对方法，本次研究通过对 Pubmed, Google Scholar 以及 Cochrane 进行系统性搜索，最终入选 11 篇研究 PCI 患者采用阿司匹林脱敏疗法的文章并对其涉及的 283 例患者进行分析研究。在所有研究中，仅 1 项研究进行了静脉脱敏疗法，该研究结果显示静脉脱敏疗法较口服脱敏疗法更高效 (98%)，并且不良反应更少。综合各项研究结果发现，采用口服脱敏疗法时，剂量递增次数 < 6 次与 > 6 次疗效没有显著区别 [95.8% (95.4%-96.2%) vs. 95.9% (95.2%-96.5%) ]，但是剂量递增次数 < 6 次时，出现皮疹和血管性水肿的情况更多 [2.6% (1.1%-4.1%) vs. 2.6% (1.9%-3.2%) ]。

在调查中，共收集到来自欧美的 86 名心脏病专家的回复，94%的专家表示阿司匹林过敏在患者中出现的概率 < 10%，最常见的症状是荨麻疹，其次为哮喘样反应和血管性水肿。令人意外的是，其中 56%的专家仍采用更换治疗方案的方式来管理阿司匹林过敏的患者，如改为氯吡格雷单药治疗或吲哚布芬，仅 42%的被调查专家会采取阿司匹林脱敏疗法。

通过本次研究及调查，我们了解到阿司匹林过敏问题在需要使用阿司匹林的冠脉综合征