

Xience V (Promus) Drug-Eluting Coronary Stent

Design features, preclinical data, and clinical outcomes.

BY KRISHNA SUDHIR, MD, PhD, FRACP, FACC; DAVID R. RUTLEDGE, PHARM D, FAHA, FCCP;
ALENA PECHONKINA, MD; AND CHUCK SIMONTON, MD, FACC, FSCAI

Drug-eluting stents (DES) are the preferred treatment for occlusive coronary artery disease, particularly in terms of antirestenotic efficacy as well as long-term safety.¹ First-generation DES have demonstrated efficacy by reduction in restenosis and target lesion revascularization (TLR). The Xience V (Promus) Everolimus Eluting Coronary Stent System (Abbott Vascular, Santa Clara, CA; Boston Scientific Corporation, Natick, MA) is considered the next-generation DES designed to be more deliverable and shown to be safe, while maintaining efficacy in a broad patient population compared with first-generation DES.² Promus is a private-labeled version of Xience V Everolimus Eluting Coronary Stent System, manufactured by Abbott and distributed by Boston Scientific. Described in this article are the design rationale, a summary of the preclinical observations, and an overview of the SPIRIT family of clinical data on Xience V (Promus).

The rapid acceptance of first-generation DES when first introduced, combined with the more recent concerns over late-stent thrombosis, were drivers in the development of a newer or second-generation of DES.

DESIGN OVERVIEW

Stent and Stent Balloon Delivery System

The Multi-Link Vision stent is made from a cobalt-chromium (Co-Cr) alloy, which allows for a thinner strut with preserved radial force and fluoroscopic visibility during deployment. With a strut thickness of 81 μm , it has the thinnest coronary stent struts on the US market.² In addition, the open-cell and nonlinear link design makes the stent flexible and conformable to the vessel wall.² The Multi-Link

Vision stent delivery balloon is made of semicompliant polyether block amide material with short tapers intended to minimize injury outside of the stented region.

Everolimus

The drug everolimus, manufactured by Novartis Pharma AG (Basel, Switzerland), is an antiproliferative agent that acts on a wide range of cell types, including vascular smooth muscle cells, which it inhibits at a low nanomolar level ($\text{IC}_{50}=0.9\text{--}3.6\text{ nM}$ for bovine smooth muscle cells) in the G1 phase of the cell cycle.^{3,4} The combination of smooth muscle cell inhibition, high potency, and high lipophilicity makes the drug an attractive candidate for controlled delivery from a DES for the prevention of neointimal hyperplasia. Preclinical studies conducted by Abbott led to the selection of a low drug dose of 100 $\mu\text{g}/\text{cm}^2$ for testing. The total dose of everolimus on a single Xience V (Promus) stent currently, as represented by the 3-X 18-mm size, is .088 mg (88 μg). The stent releases approximately 80% of the drug in 1 month, with near 100% drug release by 4 months.² This drug dose is the lowest of all the commercialized “olimus” DES products.²

Abbott elected to use a molecular entity that had been previously approved for use in humans by various regulatory bodies around the world. Furthermore, everolimus has been studied extensively by both Abbott, as the manufacturer of Xience V (Promus), and independently by scientific investigators⁵ to satisfy the evidentiary standard necessary to support the safety and efficacy profile demanded of a DES. Results have been published comprehensively and broadly in the medical literature.⁶

Xience V (Promus) Coating

Xience V (Promus) uses a two-layer coating construct composed of a primer layer and a drug-polymer reservoir layer with no topcoat. Poly(n-butyl methacrylate) is used as the thin, primer adhesion layer, and the drug reservoir layer is composed of poly(vinylidene fluoride co-hexafluoropropylene) combined with everolimus. This two-layer coating is designed for adhesion of the drug matrix to the stent and intended to minimize unwanted adhesions to the delivery balloon. The drug reservoir layer holds the drug onto the stent, controls the drug release, and contributes to the blood and vascular tissue compatibility of the DES stent.² Due to their hemocompatibility and biocompatibility, fluorinated polymers enjoy wide application in arterial prostheses, graft prostheses, drug-eluting leads of implantable cardioverter defibrillators, hemodialysis membranes, vascular and neurovascular sutures, guidewire coatings, and in guiding catheters.⁸ Maintaining the integrity of the coating in a thin layer was a key design criterion for maintaining elasticity so that the DES expanded without cracking, tearing, or webbing.⁸ Abbott selected a semicrystalline, but flexible, fluorinated polymer, the design of which included a primer and drug reservoir construct as well as a solvent-drug-polymer formulation for maintaining a consistent coating for Xience V (Promus).²

PRECLINICAL STUDIES

Abbott conducted extensive preclinical studies as a basis for selecting a polymer, clinical dosing, pharmacokinetic profiling, and for testing the safety of single stents and overlapping stents. Maximum dose was determined by two animal models—the porcine coronary arterial model and rabbit iliac model—followed from 4 weeks to 2 years. Morbidity and mortality rates for all preclinical studies were <1%, while complete endothelialization by 28 days sequestration of struts within a benign, fibromuscular neointima, a widely patent lumen, and inflammation comparable to Multi-Link Vision was shown. Furthermore, vascular responses were parallel to the system's pharmacokinetics, with complete vascular healing by 6 months in accordance with complete everolimus elution.² Everolimus was released in a controlled manner for 120 days and remained primarily localized within the stented arterial region. Thrombosis, malapposition, medial loss, or other adverse effects were not observed in any preclinical studies. Safety in the preclinical studies was established with data generated in two species over a period of 2 years.⁹

XIENCE V (PROMUS) CLINICAL EXPERIENCE

The SPIRIT family of trials is a clinical program that will

include more than 16,000 patients with more than 14,000 patients assigned to Xience V (Promus). This global clinical trials program consists of eight studies that have either completed enrollment, are currently enrolling, or are designed as postapproval studies.

Initial clinical safety and performance of Xience V (Promus) was demonstrated in the SPIRIT FIRST clinical trial, a randomized, controlled, single-blinded evaluation of Xience V (Promus) in the treatment of patients with de novo native coronary artery lesions.¹⁰ A total of 60 patients (28 in the Xience V [Promus] treatment group and 32 in the Multi-Link Vision bare-metal stent control group) were enrolled at nine investigational sites outside the US. The primary endpoint was in-stent late loss at 6 months. The SPIRIT FIRST trial showed a statistically significant outcome for Xience V (Promus) over the bare Multi-Link Vision stent. In-stent late loss of 0.1 ± 0.23 mm in the everolimus-eluting stent group represented an 88% reduction relative to the control group (0.84 ± 0.36 mm) ($P < .001$). A low 6-month major adverse cardiac event (MACE) (the composite endpoint composed of cardiac death, myocardial infarction [MI], or clinically driven target site revascularization) rate of 7.7% supported the clinical safety parameters for Xience V (Promus). The SPIRIT FIRST trial showed that the clinical safety observed at 6 months was sustained out to 4 years, as demonstrated by no observations of late-stent thrombosis events and continued low target vessel failure (TVF) (the composite endpoint composed of cardiac death, MI, or clinically driven target vessel revascularization [TVR]) and MACE rates.¹⁰

The SPIRIT II clinical trial conducted in Europe was a continuation in the assessment of the safety and performance of Xience V (Promus) versus Boston Scientific's Taxus Paclitaxel-Eluting Coronary Stent System. Patients with a maximum of two de novo native coronary artery lesions located in two different epicardial vessels (from 2.5 to 4.25 mm in diameter and up to 28 mm in length, including overlapping stents) were treated with Xience V (Promus).¹¹ The 300 subjects enrolled into the SPIRIT II clinical study were from 28 international sites. Of the 300 subjects enrolled, 223 were randomized to receive Xience V (Promus), and 77 were randomized to receive Taxus (3:1; Xience V [Promus]:Taxus randomization); of the 77 patients, 59 received Boston Scientific's Taxus Express², and 17 received Boston Scientific's Taxus Liberté. One patient received a nonstudy stent. Twenty-seven percent of the Taxus lesions received Taxus Liberté stent.¹² The primary endpoint was in-stent late loss at 6 months. The data indicated that Xience V (Promus) was superior to Taxus for in-stent late loss at 6 months. Xience V (Promus) in-stent late loss was 0.11 mm, whereas Taxus in-stent late loss was 0.36 mm, which represents a 69%

reduction in late loss. Lower rates on key clinical endpoints were observed for Xience V (Promus) compared to the Taxus arm, such as ischemia-driven MACE (2.7% and 6.5%, respectively) and protocol-defined late-stent thrombosis (0.5% and 1.3%). Ischemia-driven MACE at 180 days was sustained through 1 year for Xience V (Promus), and no new instances of late-stent thrombosis were observed in either group at 1 year.

Two-Year Key Clinical Outcome Results

The key clinical outcomes of the SPIRIT II randomized controlled trial (RCT) at 2-year follow-up demonstrated that Xience V (Promus) at 1 year and 2 years resulted in lower observed rates of ischemia-driven MACE and ischemia-driven TLR in the Xience V (Promus) arm compared to the Taxus arm.¹³

For key clinical endpoints, the following results were obtained. The ischemia-driven TLR rates were 3.8% in the Xience V (Promus) arm and 6.8% in the Taxus arm ($P=.33$). The ischemia-driven MACE rates were 6.6% in the Xience V (Promus) arm and 11% in the Taxus arm ($P=.31$). Cardiac death rates were 1.4% for Taxus and 0.5% for Xience V (Promus) ($P=.45$), whereas MI rates at 2 years were 5.5% for Taxus and 2.8% ($P=.29$) for Xience V (Promus). Low stent thrombosis rates (Academic Research Consortium [ARC] definite/probable) were observed for Xience V (Promus) at 2 years (Xience V [Promus] 0.9%, Taxus 1.4%). A modest increase in late loss and neointima was observed in the Xience V (Promus) arm over time.

The SPIRIT III clinical trial was designed as the pivotal trial in the US to demonstrate safety and effectiveness of Xience V (Promus).¹⁴ SPIRIT III was a prospective, randomized, active-controlled, single-blinded, parallel two-arm multicenter clinical trial using either the Xience V (Promus) stent on a rapid exchange delivery system or the FDA-approved, commercially available Boston Scientific Taxus Express² Paclitaxel-Eluting Coronary Stent System. The protocol allowed for dual-vessel treatment and planned stent overlap.

The SPIRIT III RCT study enrolled 1,002 subjects (randomized 2:1 Xience V [Promus]:Taxus Express²) at 65 sites in the US.² The primary endpoint for the SPIRIT III RCT was in-segment late loss at 240 days, and the major secondary endpoint was ischemia-driven TVF at 270 days. Xience V (Promus) in-segment late loss at 240 days was 0.14 mm compared to Taxus Express² in-segment late loss of 0.28 mm. These data demonstrated noninferiority ($P<.001$) and superiority ($P=.004$) for Xience V (Promus) in terms of in-segment late loss at 240 days. Xience V (Promus) was also found to be noninferior ($P<.001$) to Taxus Express² in terms of the major second-

ary endpoint, with ischemia-driven TVF rates of 7.2% and 9%, respectively. The rates of late stent thrombosis through 393 days for Xience V (Promus) versus Taxus Express² were 0.3% versus 0.6% by protocol definitions and 1.1% versus 0.6% by the Academic Research Consortium (ARC) definitions (definite plus probable).¹⁴

The primary endpoint for the SPIRIT III 4-mm, nonrandomized arm was in-segment late loss at 240 days. The Xience V (Promus) 4-mm, nonrandomized arm in-segment late loss was 0.17 mm and is noninferior ($P<.0001$) to the Taxus Express² in-segment late loss of 0.28 mm. The Xience V (Promus) in-segment late loss in the 4-mm arm is comparable to the Xience V (Promus) in-segment late loss in the SPIRIT III RCT.²

Two-Year Follow-Up

At a 2-year follow-up, SPIRIT III continued to demonstrate a consistent profile as reported through 1 year, as shown by the lower rates of TVF, MACE, TLR, and TVR in the Xience V (Promus) arm compared to the Taxus Express² arm.¹⁵

The TVF rates at 2-year follow-up were 10.7% in the Xience V (Promus) arm compared to 15.4% in the Taxus Express² arm, a relative reduction of 31% in TVF rates in favor of the Xience V (Promus) stent ($P=.04$). The MACE rates at 2 years were lower for the Xience V (Promus) arm (7.3%) compared to the Taxus Express² arm (12.8%), a reduction of 43% in favor of the Xience V (Promus) stent ($P=.004$). The rates for TLR were also lower in Xience V (Promus) (4.3%) compared to Taxus Express² (6.9%) ($P=.07$). There was also a trend in reduction of all death and MI at 2 years in favor of Xience V (Promus) (4.7 vs 7.8; $P=.052$), thus showing low clinical events were sustained at 2 years.¹⁵ Stent thrombosis rates through 2-year follow-up were numerically lower for Xience V (Promus) compared to Taxus Express², for both the protocol (1% vs 1.7%) and ARC (1.3% vs 1.7%) definitions of stent thrombosis (Figure 1).

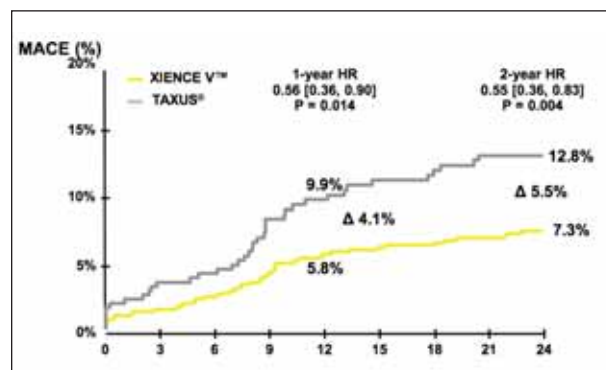


Figure 1. Two-year MACE data from SPIRIT III. Adapted from Stone GW. Presented at EuroPCR 2008.¹⁵

TABLE 1. OVERVIEW OF TOTAL XIENCE V (PROMUS) SPIRIT FAMILY ENROLLMENT

	Total (Xience V [Promus] + Control)	Xience V (Promus)	Planned Follow-Up
SPIRIT FIRST	60	28	5 y
SPIRIT II	300	223	5 y
SPIRIT III	1,002	668	5 y
SPIRIT IV	3,690	2,460	5 y
SPIRIT V	3,000	2,900	5 y
XIENCE V (Promus) SPIRIT WOMEN	2,000	1,850	5 y
XIENCE V (Promus) India	1,000	1,000	5 y
XIENCE V (Promus) USA	5,000	5,000	5 y
Total	16,052	14,129	

Clinical pharmacokinetic substudies were conducted in three different geographies to demonstrate the elution of everolimus from the Xience V (Promus) stent. SPIRIT II (conducted outside the US) and SPIRIT III (conducted in the US [RCT] and Japan [registry]) contained pharmacokinetic substudies. The pharmacokinetic profile for everolimus eluted from the Xience V (Promus) stent is consistent across all geographies, which pharmacokinetic profile shown to be consistent with the preclinical profile.

The studies also show consistent angiographic, clinical, and pharmacokinetic results for Xience V (Promus) across all geographies. Abbott seeks to enroll 13,000 additional patients for four planned continued-access/postapproval studies and one postapproval surveillance registry.²

The SPIRIT IV clinical trial is a continued-access study initiated on August 14, 2006, to further evaluate the safety and effectiveness of the Xience V (Promus) and to enroll SPIRIT III-like subjects to support the SPIRIT III major secondary endpoint (270-day TVF). SPIRIT IV is a single-blinded, multicenter clinical trial that enrolled 3,690 subjects at 66 sites in the US.¹² This trial is randomized (2:1 Xience V [Promus]: Taxus Express²) in subjects with a maximum of three de novo native coronary artery lesions, maximum of two lesions per epicardial vessel, and in some cases, lesions that are located at areas of bifurcation, with reference vessel diameters (RVD) ≥ 2.5 mm to ≤ 4.25 mm and lesion lengths ≤ 28 mm. Overlapping stents were allowed for Xience V (Promus) subjects with lesions > 22 mm. The primary endpoint of the trial is ischemia-driven MACE at 270 days. Patients will be followed out to 5 years.² This study completed enrollment in July 2008.

SPIRIT V is an international (outside the US) study with a target of 3,026 patients. Of these, 2,701 patients com-

pleted enrollment in November 2007 in a registry assessing a composite endpoint of death, MI, and TVR with 5-year follow-up. ARC-defined stent thrombosis and other clinical outcome parameters will also be evaluated. An additional 325 patients with diabetes will be enrolled in a randomized study of Xience V (Promus) versus Taxus Express² in a 2:1 randomization with a 9-month angiographic endpoint of late loss.¹⁶

XIENCE V SPIRIT WOMEN is a 2,000 female patient all-comers study being conducted in Europe and countries in the Asia-Pacific region. Of these participants, 1,550 will be enrolled in a single-arm registry assessing a composite endpoint of death, MI, and TVR with 5-year follow-up. ARC-defined stent thrombosis and other clinical parameters will also be studied. Additionally, 450 patients will participate in a trial of Xience V (Promus) versus the Cypher Stent (Cordis Corporation, Warren, NJ) in a 2:1 randomization with a 9-month endpoint of angiographic late loss. Enrollment commenced in July 2007, and follow-up will be for 5 years.²

In clinical trials, a patient-reported quality-of-life outcome instrument can be used to measure the effect of an intervention on several aspects of patient health status. Recently, data from the Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE) trial suggest that stenting has no additional benefits over drug therapy in improving life-threatening outcomes in a selective study population with coronary artery disease. However, quality-of-life data obtained during this trial using the Seattle Angina Questionnaire (SAQ) indicate the proportion of angina-free patients was significantly higher at 1 and 3 years in the percutaneous coronary intervention group with lower antiangina

medication use.¹⁷ The validated SAQ will be administered as part of a global surveillance program in order to determine treatment effects on patient-assessed outcomes using the patient as his own control.¹⁸

XIENCE V India is a 1,000-patient registry of all-comers in India. Follow-up is for 5 years. The study protocol is similar to that for the US postapproval registry, XIENCE V USA, which will assess ARC-defined stent thrombosis, device-oriented and patient-oriented outcomes, patient compliance and therapy interruptions with dual-antiplatelet therapy, major bleeding complications, clinical device and procedural success, and patient health status using the SAQ.² Enrollment commenced in May 2008.

Finally, XIENCE V USA is a 5,000-patient postapproval registry with 5-year follow-up. This study is a prospective, open-label, multicenter, observational, single-arm registry for evaluating Xience V (Promus) during commercial use in real-world settings. Physicians with a range of coronary stenting experience will be invited to participate. The study will assess ARC-defined stent thrombosis, device-oriented and patient-oriented outcomes (including death, MI, and revascularization), patient compliance and therapy interruptions with dual-antiplatelet therapy, major bleeding complications, clinical device and procedural success, and patient health status using the SAQ. Enrollment commenced in July 2008, and follow-up will be for 5 years.²

In total, the XIENCE V SPIRIT family of trials provides comprehensive evaluation of more than 16,000 patients worldwide (Table 1).

CONSISTENCY ACROSS TRIALS

The results for in-stent and in-segment late loss, TVF, MACE, cardiac death, and MI are consistent across all studies and all geographies.

CONCLUSION

The clinical programs and data derived indicate the clinical superiority for Xience V (Promus) compared to Taxus Express², which is also consistent with the design of the stent, the dose of the drug, and the nature of the polymer. A comprehensive program designed to understand the long-term safety of the product, particularly with respect to stent thrombosis is planned to include 14,000 patients followed over a period of 5 years. Detailed information on the performance of Xience V (Promus) in women will be collected, as well. Finally, assessments of patient-reported outcomes in real-world settings are being assembled for the purpose of yielding valuable experiential data for the user population. ■

Krishna Sudhir, MD, PhD, FRACP, FACC, is Medical Director of Global Clinical Science at Abbott Vascular and Consulting

Associate Professor of Medicine at Stanford University in Palo Alto, California. He has disclosed that he is a salaried employee of and shareholder in Abbott Vascular. Dr. Sudhir may be reached at (408) 845-3370; krishna.sudhir@av.abbott.com.

David R. Rutledge, Pharm D, FAHA, FCCP, is Director of Global Clinical Affairs at Abbott Vascular. He has disclosed that he is a salaried employee of and shareholder in Abbott Vascular. Dr. Rutledge may be reached at (408) 845-3820; david.rutledge@av.abbott.com.

Alena Pechonkina, MD, is Principal Clinical Research Scientist at Abbott Vascular. She has disclosed that she is a salaried employee of Abbott Vascular. Dr. Pechonkina may be reached at (408) 845-1378; alena.pechonkina@av.abbott.com.

Chuck Simonton, MD, FACC, FSCAI, is Chief Medical Officer of Abbott Vascular. He has disclosed that he is a salaried employee of and shareholder in Abbott Vascular. Dr. Simonton may be reached at (408) 845-1857; charles.simonton@av.abbott.com.

1. Sheiban I, Villata G, Bollati Mario, et al. Next-generation drug-eluting stents in coronary artery disease: focus on everolimus-eluting stent (Xience V). *Vascular health and risk management* (New Zealand) 2008;4:31-38.
2. This data was presented by Abbott Vascular to the US Food and Drug Administration Circulatory System Devices Advisory Panel on Xience V (Promus). Washington, DC. Nov 29, 2008. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=687> Accessed September 1, 2008. This statement does not reflect any position by the US FDA or acceptance of the data presented.
3. Schuler W, Sedrani R, Cotton S, et al. SDZ RAD, a new rapamycin derivative. *Transplantation*. 1997;64:36-42.
4. Pedrini L, Dondi M, Magagnoli A, et al. Evaluation of thrombogenicity of fluoropassivated polyester patches following carotid endarterectomy. *Ann Vasc Surg*. 2001;15:679-683.
5. Biondi-Zoccai G, Lotrionte M, Moretti C. Percutaneous coronary intervention with everolimus-eluting stents (Xience V): systematic review and direct-indirect comparison meta-analyses with paclitaxel-eluting stents (Taxus) and sirolimus-eluting stents (Cypher). *Minerva Cardioangiol*. (Italy) 2008;56:55-65.
6. Dunn C, Croom KF. Everolimus: a review of its use in renal and cardiac transplantation. *Drugs*. (New Zealand) 2006;66:547-70.2.
7. US Department of Health and Human Services Food and Drug Administration. Center for Devices and Radiological Health (CDRH). Center for Drug Evaluation and Research (CDER). Guidance for Industry. Coronary Drug-Eluting Stents. March 9-10, 2008. Available at <http://www.fda.gov/cdrh/ode/guidance/6255.pdf>. Accessed September 9, 2008.
8. Graftie K. Fluoropolymers: fitting the bill for medical applications. *MD&DI*. 2005;34-37.
9. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol*. 2008;52:333-342.
10. Serruys PW, Ong AT, Piek JJ. A randomized comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: the SPIRIT First trial. *EuroIntervention*. 2005;1:58-65.
11. Serruys P, Ruygrok P, Neuzner J, et al. A randomized comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. *EuroIntervention*. 2006;3:286-294.
12. Data on file at Abbott Vascular.
13. Clinical Evaluation of the XIENCE Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions Clinical, Angiographic and IVUS 2 year results. Serruys PW. Presented at: SCAI-ACC12 Late-Breaking Clinical Trials III: DES. Chicago, IL. March 31, 2008.
14. Stone GW, Midei M, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA*. 2008;299:1903-1913.
15. SPIRIT III. A prospective, randomized trial comparing an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease. 2-year clinical follow-up. Stone GW, for the SPIRIT III Investigators. Presented at: EuroPCR 2008. Barcelona, Spain. May 15, 2008.
16. Relevance of Early Outcome Data after DES—Insights from SPIRIT V, Grube, E. Presented at: European Society of Cardiology. Munich, Germany. August 2008.
17. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.
18. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med*. 2008;359:677-687.