Washington State Health Care Authority

Health Technology Assessment Program

Health Technology Clinical Committee

May 2009 Meeting

Washington's Health Technology Assessment Program Background

- **Part of Governor's 2006 Five point health strategy for state to lead by example**
  - **Emphasize evidence-based health care**

http://www.hca.wa.gov/contf/doc/GovGregoireHealthBrief.pdf

- **Program Purpose: Achieve better health by paying for technologies that work**
  - Better health with better information: investigate what works and maintain a centralized website.
  - Open and transparent process: publish process, criteria, reports, and committee decisions in public meeting.
  - Eliminate Bias: contract for independent evidence report and independent clinical committee.
  - Promote consistency: state agencies rely on a single, scientifically based source.
  - Flexible: review evidence regularly to ensure update information is included.

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- Overall Issue: WA citizens pay high cost for health care and receive poorer outcomes
- Government Issue: Public Programs have limited and/or shrinking resources and rising costs and needs.
- Common reaction: Reduce Eligibility, Rates or Benefits
  - "Thin the soup or cut the line"

Vision: Transform WA state from a passive payer to an active purchaser of higher quality, more efficient health care

- Action: Ensure WA pays for technologies that are proven safe, effective and cost-effective

"Better ingredients in the soup make it go farther"

HTA Goal

Outcome: Pay for What Works

- Coverage decisions:
  - scientifically based
  - use transparent process, and
  - consistent across state health care purchasing agencies

- Formal, systematic process to identify, review, and cover appropriate health care technologies.
  - Is it safe?
  - Is it effective?
  - Does it provide value (improve health outcome)?

HTA Program – Ongoing Operations

Pay for What Works: Better Information is Better health

- Topic Selection
  - No updates 2009 selections underway
- Coverage Decisions
  - CCTA Finalization
- Evidence Reports Underway
  - Bone Growth Stimulation
  - Calcium Scoring
  - Vagus Nerve Stimulator
  - Hip Resurfacing
- Evidence Reports Not yet started
  - Sleep Apnea Diagnosis and Treatment
  - Glucose Monitoring

HTA Program – Ongoing Operations

Pay for What Works: Better Information is Better health

- Clinical Committee
  - Appointment for vacancies complete - Welcome
    - Megan Morris
    - Dr. Chris Standaert
- Program Operations
  - Governor - Program mentions
    - HTA featured in several presentations including White House Regional Health Reform
  - Legislative session
    - HTA requested to give two work-session updates and several legislator briefings
    - Bill for Proposed program changes did not pass committee
  - HTCC member included in new legislatively created committee for evidence based radiology guidelines

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Topic Selection and Decision Process

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Process Overview

1. HCA Administrator Selects Technology

Nominate, Review, Public Input, Prioritize

Semi-annual

2. Vendor Produce Technology Assessment Report

Key Questions and Work Plan, Draft, Comments, Finalize

2-8 Months

3. Clinical Committee makes Coverage Determination

Review report, Public hearing

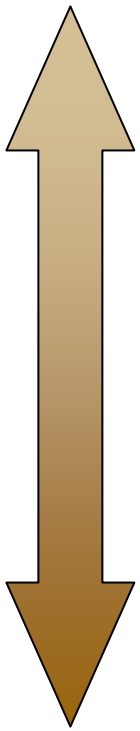
Meet Quarterly

4. Agencies Implement Decision

Implements within current process unless statutory conflict

Hierarchy of Evidence

Best: Meta-analysis of large randomized head-to-head trials.



Large, well-designed head-to head randomized controlled clinical trials (RCT):

- Long-term studies, real clinical endpoints
- Well accepted intermediates
- Poorly accepted intermediates

Smaller RCTs, or separate, placebo-controlled trials

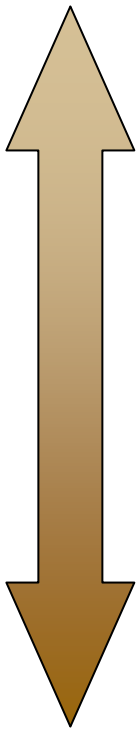
Well-designed observational studies, e.g., cohort studies, case-control studies

Safety data without efficacy studies

Case series, anecdotes

Least: Expert opinion, non-evidence-based expert panel reports, and other documents with no direct clinical evidence

Evidence in Health Care Decision Making



- **Level 3:** *"What would I recommend to the state or nation?"*
  - **Must be based on rigorous assessment of the scientific evidence.**
  - **Affects hundreds of thousands, even millions of people.**
- **Level 2:** "*What would I recommend to my patient/client?"*
  - Influenced by prior experience, but the scientific evidence may play a greater role.
  - Affects possibly hundreds of people.
- **Level 1:** *"Would you have this done for yourself or for someone else in your immediate family?"*
  - Influenced by one's personal experience with the disease and capacity to deal with risk.
  - Affects few people.

Used with Permission from Dr. Mark Helfand, OHSU

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Evidence for use in Policy Decisions

Different Data Sources

- Efficacy
  - How technology functions in “best environments”
    - Randomized trials-distinguish technology from other variables
    - Meta-analysis
- Effectiveness
  - How technology functions in “real world”
    - Population level analyses
    - Large, multicenter, rigorous observational cohorts (consecutive pts/objective observers)
- Safety
  - Variant of effectiveness
    - Population level analyses
    - Case reports/series, FDA reports
- Cost
  - Direct and modeled analysis
    - Administrative/billing data (charge vs cost)
- Context
  - Mix of historic trend, utilization data, beneficiary status, expert opinion

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Cardiac Stent Topic

Cardiac Stent Topic

- Brief background relevant to policy issues
  - Disease and Diagnosis
  - Treatments
  - Selected Technology
- Agency Prioritization Criteria and Concerns
- Key Questions
  - Initial and Revised
- Medicare Coverage Decision
- Treatment Guidelines

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Topic Background: Disease/Diagnosis

- Heart disease, specifically coronary heart disease (CHD) is an important public health concern.
- CHD is a narrowing or blockage of one or more coronary arteries with plaque.
- CHD is very prevalent and patients with the disease range from no symptoms to chest pain (angina), to heart attack- myocardial infarction (MI), or death.
- Prediction of risk and symptoms is difficult.
  - location and severity of obstructions are used but, especially severity is not always correlated with symptoms or outcomes

Bottom line: lots of people have it; many have no symptoms; some at grave risk but unclear who

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Topic Background: Treatments

- Treatment to open arteries and relieve symptoms and health risks include:
  - Manage and reduce risk factors – smoking, obesity, high blood pressure/cholesterol
  - Medication therapy: beta blockers, nitrates, statins, calcium channel blockers and antiplatelet agents
  - Surgical treatment by mechanically opening the artery with a catheter with/without stent (percutaneous coronary intervention PCI) and bypass surgery
- Use of PCI has steadily risen over past decade while bypass remains relatively unchanged and PCI accounts for over 60% of surgical treatment.
- Unanswered questions remain about best use of each option, when, and for what patients.

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Topic Background: Selected Topic

- Cardiac stents are small tubes placed in an artery to keep it open. Stents are either not coated (bare metal stents) or coated with a drug (drug eluting stents)
- Stent advantages include physically opening the artery and being less invasive than bypass surgery
- Stent disadvantages include targeted solution to widespread disease, unclear protocols, clotting and re-operation
- Important, unanswered questions remain about whether and when stent placement is appropriate versus other medical management or surgery.
  - What patient, disease level, and timing are best for this invasive procedure

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Topic Background: Selected Topic

- Current FDA approval for cardiac stents is for the placement of a single stent in a new lesion occurring in arteries of a specific size.
- In general, for non-acute situations, clinical guidelines indicate stent placement is appropriate after a trial of optimal medical therapy and where documented evidence of ischemia exists, but do not limit use to single stent or certain disease severity or location
- In practice, stenting is now routinely performed in patients with varying disease levels, locations, and symptoms.
- In acute situations, stenting is also performed outside FDA indications.

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Agency Prioritization

- **Safety concern: High**
  - Primary safety concerns: long term risks, procedure risks, frequency, FDA panel findings on thrombosis for DES off label.
- **Efficacy concern: High**
  - Primary concerns: efficacy of stenting to prevent death or major cardiac event and high stent diffusion with low or mixed evidence on appropriateness
  - Concerns about high use variation especially 70% non-FDA approved uses in generally sicker or more complicated patients; drug eluting stent use; use instead of optimized medical therapy in lower risk patients and instead of CABG in high risk patients;
- **Cost Concern: Medium**
  - Cost concerns reflect mainly concern about over or mis-utilization, and wide cost differences between treatment choices.

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Key Questions

- **Key Question Function**
  - Sets parameters for research inquiry and policy decision
- **Key Question Components**
  - Legislatively, key questions are centered on a technology's evidence of safety, efficacy, effectiveness, and cost and application in any special population
  - Methodologically, questions are refined to include a defined population, intervention, comparator(s), and outcome (PICO)
- **Cardiac Stent Focus**
  - The overall question related to cardiac stents is what is the evidence of safety, efficacy, effectiveness and cost
    - For patients with CHD, including any studied special population,
    - undergoing stenting,
    - compared to medical management or bypass surgery,
    - in treating patient oriented outcomes of symptom relief, major cardiac event, and death

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Key Questions

- **Key Question – Cardiac Stent**
  - Stent usage is established and has a large amount of literature supporting some use
  - The policy question for state agencies is thus focused on most appropriate use balancing harms, benefits, and costs
  - Consultation and feedback from industry; providers; the evidence vendor and clinical consultant indicated that this topic was still too broad for an evidence review.
- **Initial Stent Focus**
  - A smaller topic that addressed one area of significant safety and effectiveness concern is the placement of stents in non-FDA approved indications (up to 70% of usage)
    - specifically multiple stent placement is one of the largest categories and literature is available

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Key Questions

- **Cardiac Stent Research Issues**
  - Stent studies vary in patient population and disease level and do not specifically focus on efficacy of non-FDA approved uses, and may not categorize multiple stent placement separately or use same definitions
  - These methodological as well as other clinical and timing issues significantly increase report time and scope and potentially could result in an evidence report without meaningful analysis.

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Key Questions

- **Updated Stent Focus**
  - Direction to create overview of stent use to set context and take advantage of initial research,
  - Focus review on well defined and studied sub-topic: Bare metal stents versus drug eluting stents
    - Removes some controversy of stent question of overall when or whether to cover, focuses on which type
    - Remains significant issue due to high utilization of drug eluting stents (local and agency data about 80%)
    - Recent FDA focus on safety concerns of DES
    - Agency's cost of over $3,000 additional for DES
- **Future Topic**
  - Broader questions remain on when and in whom stents are most appropriate. May be informed by subsequent topics, reviews, or potential collaborative and other agency efforts.

Medicare Coverage and Clinical Guidelines

Medicare Coverage and Guidelines

Organization	Date	Outcome	Evidence Cited?	Grade / Rating
Medicare Pub. 100-03 WA-HTA report P.42	NR	No national coverage decision (NCD) specific to bare metal versus drug eluting stents. Overall PTA coverage memo: PTA (with and without the placement of a stent) is covered when used in accordance with FDA approved protocols for treatment of atherosclerotic lesions of a single coronary artery for patients for whom the likely alternative treatment is coronary bypass surgery and who exhibit the following characteristics: (1) angina refractory to optimal medical management; (2) objective evidence of myocardial ischemia; and (3) lesions amenable to angioplasty. Coverage for all other indications is at local Medicare contractor discretion.	No	N/A

Medicare Coverage and Clinical Guidelines

Organization	Date	Outcome	Evidence Cited?	Grade / Rating
Guidelines – WA HTA p. 41 and App. N	NA	No guidelines for clinical care or appropriateness have been published regarding the use of BMS versus DES. Most comprehensive joint ACC/AHA guidelines address broader perspective on setting and issues involved in the decisions leading to coronary stent placement.		

Cardiac Stents

Questions?

May 1, 2009

Health Technology Assessment Program
PO Box 42712
Olympia, WA 98504-2712
shtap@hca.wa.gov

Re: Final Report of Cardiac Stents

Dear program staff:

On behalf of our eight hospitals operating in Washington State, Providence Health & Services Washington/Montana Region is writing to provide comments on the Health Technology Assessment's (HTA) study comparing drug-eluting stents (DES) to bare metal stents (BMS). Providence has provided compassionate, quality care for our communities in Washington State for over 150 years and quality cardiac care for over 100 years. Providence was incorporated on January 28, 1859 – thirty years prior to Washington achieving statehood – making it the second oldest corporation in the state.

Providence prides itself in not only being a founder of compassionate care, but also being a leader in innovative care. In fact, many Providence ministries consistently rank in the top 100, or top three percent of hospitals and cardiovascular hospitals by Thomson Reuters®, demonstrating our ability to efficiently provide high-quality care.[1] Collectively, Providence is the largest provider of cardiac care – providing more cardiovascular procedures than any other organization in the state. It is with this history and commitment that we share our concerns about the possible decision to eliminate state coverage for DES. Our comments are detailed below.

Operationally Unfeasible to Implement

If the determination is made to no longer cover DES for Medicaid, public employees and their families, and other patients, this may cause an operationally unfeasible situation for the 30 hospitals in Washington State performing stenting procedures. Approximately 20 percent of stenting procedures occur in an emergent situation –

[1] According to Thomson Reuters – a national firm designed to objectively measure and compare hospitals – if all Medicare inpatients received the same level of care as Medicare patients treated in the winning hospitals: more than 107,500 additional patients would survive each year; nearly 132,000 patient complications would be avoided annually; expenses would decline by $5.9 billion a year nationwide; and the average patient stay would decrease by nearly half a day.

providing little to no time for obtaining payer information. Also, many times, Medicaid eligibility is pending and unknown when patient services are provided. In these situations, a DES will have already been placed in the patient by the time the payer coverage is known. This would leave the hospital in a position of not being reimbursed for the added costs of DES, through no fault or control of its own.

Cost Shifting Uncompensated Care

Because of the difficulty described in the previous section, when a DES is used and not paid for, this cost will be passed-on in the form of a hidden tax to the segment of the population that has health insurance coverage.[2] These additional costs place further pressure on the affordability of health care insurance.

In 2006, Premera Blue Cross commissioned an actuarial analysis by Milliman, Inc. Their study confirmed a long-held industry acknowledgment that uncompensated care costs are passed-on to other payers – known as cost shifting. Among their principal findings, in 2004, approximately 14 percent, or $490, of a typical family's insurance premium is a result of this hidden tax, covering uncompensated hospital costs. This amount is estimated to grow at one percent a year.

So to the extent that a DES is used and not *directly* paid for, these costs will be paid for in another form via this hidden tax. ***If the decision is made to no longer cover DES, Providence respectfully requests an exception be made for emergent and urgent cases where the procedure is not scheduled in advance.***

Stewardship

It is important to note that an argument to maintain DES coverage is not based on a financial motive, but rather what is best for the patient and allowing the decision-making authority to remain with the physician and his or her patient. Consistent with the findings of the final report, DES ***do*** reduce the need for repeat revascularization within the first year – thereby minimizing the future need for acute medical care and hospitalization.

Unfortunately, payment methodologies for health care in the United States generally incent quantity sick care instead of quality health care. Simply put, the more procedures performed, the more revenue is obtained by providers. Providence requests DES to remain covered because we do not want patients unnecessarily having to return in the future for revascularization resulting from BMS. Such a position may appear to be counter-intuitive for a health care provider, however, it is in fundamental accord with one of our five core values – Stewardship.

The earth is the Lord's and all that is in it. Psalm 24:1
We believe that everything entrusted to us is for the common good

[2] In 2008, less than 57 percent of full-time employees are covered with employer-sponsored health insurance in Washington State.

Sustaining the position to cover DES is altruistic and advantageous for the state. ***Providence respectfully requests HTA allow physicians the tool required (DES), when needed, to provide the best possible care and reduce the need for repeat procedures.***

Two-tiered Outcome

Providence fears a two-tiered cardiovascular health care result stemming from a decision to not cover DES. Medicare beneficiaries, those with commercial health insurance, and private pay patients will all have the option to receive either a DES or BMS, depending on their situation. The poor and disabled, however, as well as public employees and their families will only be allowed to receive a BMS. Providence is concerned at the potential ramifications resulting from this two-tiered approach given the findings of benefits from DES.

Physicians and patients choose stent types based upon the patient's condition and individualized care needs. Physicians should have the option to use this valuable and technologically advanced tool when conditions permit. ***Providence urges HTA to maintain DES as a covered benefit.***

If you have any questions, please contact me at William.Callicoat@Providence.org or by phone at (360) 486-6651.

Sincerely,

[redacted]

William Callicoat
Director of Health Care Policy
Washington/Montana Region
Providence Health & Services

Cc: John Fletcher
Dr. Michael E. Ring, MD, FACC, FSCAI
Mike Marsh
Chuck Hawley
Tom Brennan
Patty Degroodt
Kurt Miller

Comments to Washington State Health Care Authority on HTA Report - Cardiac Stents: Comparison of Drug Eluting Stents with Bare Metal Stents

May 8. 2009

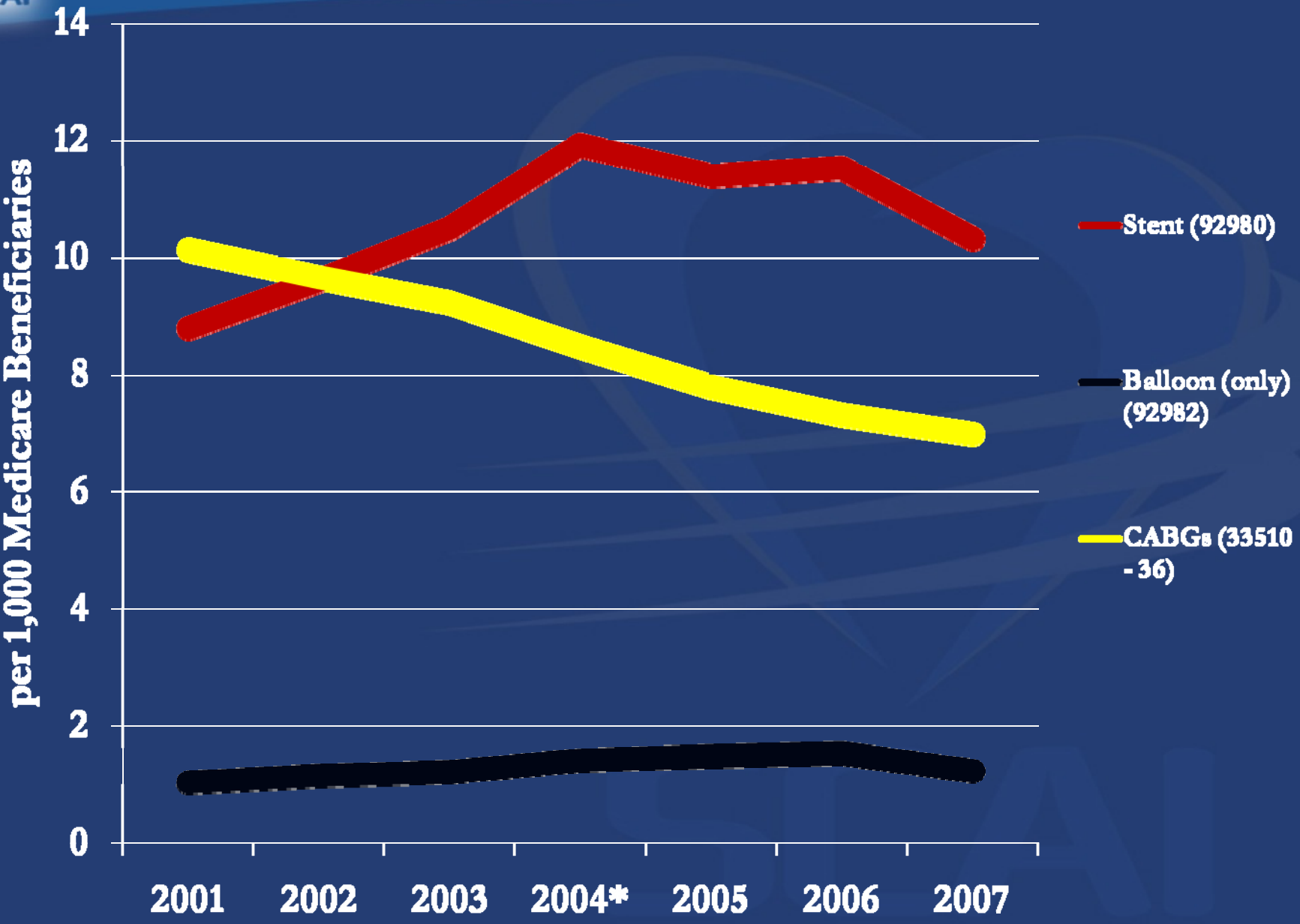
Wayne Powell

Sr. Director for Advocacy and Guidelines

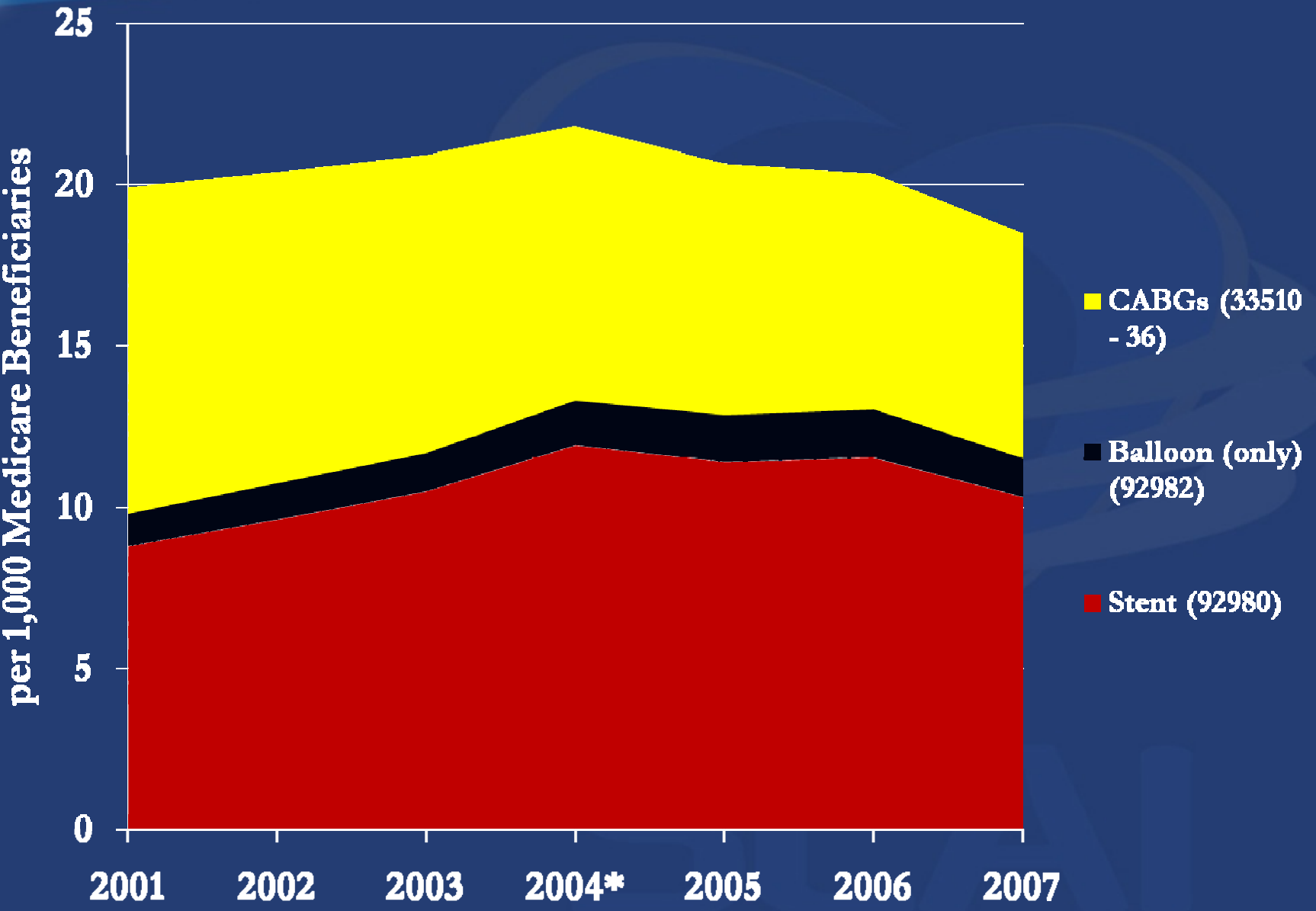
Disclosure of Relationships

- No financial relationship with any health care entity
- Employed by professional association for interventional cardiologists (whose pay doesn't vary by type of stent used)
- SCAI does get some funding from organizations that make both BMS and DES

Invasive Cardiac Procedures In Medicare



Invasive Cardiac Procedures In Medicare



Cost Effectiveness Analysis is Difficult

- HTA reviewed 48 research efforts and found significant weaknesses in most
- Good suggestions for future analysis made on page153
- What is the situation in Washington State?

Washington State Data

- Significant costs may be missed
  - pre-procedure testing and consultation
  - physician procedure fees

Counting the number of procedures

- Additional CPT codes billed with extra vessels – but those aren't extra procedures
- Some procedures staged for clinical reasons
- Some procedures are hybrids (different types of stents)

Pre-procedure costs

- Additional time and effort with patient to assure that they can comply with dual anti-platelet therapy
- Fewer ad-hoc procedures (which cost less) - because of need to consult with patient about their appropriateness for DES.

Alternative Treatment Options

- CABGs (more expensive initially or for restenosis)
- Medical Therapy (costs unknown but 1/3 crossed-over anyway in COURAGE)

Measuring Intra Procedure Costs is Very Difficult

- Costs vary by procedural setting
- Costs vary over time
- Costs are not charges
- Two stents cost more (sometimes)
- Different types of stents are used in same procedure (sometimes)

Post Procedure Costs Vary

- Physician follow-up costs may vary by type of stent (and are not included because this is not a global procedure)
- Follow-up diagnostic imaging costs

Costs Vary Over Time

- PCI procedures are moving to less expensive outpatient settings
- Clopidogrel going off patent
- Prasurgagrel approval recommended by FDA panel
- Price competition among growing number of DES manufacturers and products may affect prices

Repeat Revascularization Costs Vary

- Which type of revascularization? (CABG vs. PCI)
- Disability
- Testing to establish need for repeat procedure
- Physician fees (HTA data seems to look only at hospital payments)
- Additional costs of anti-platelet therapy extension

Whose Costs are we Talking About Anyway?

- State - employee health care costs
- State - lost employee productivity
- Patient's co-insurance and deductibles (sometimes paid by third parties)

Conclusion

- Does the Washington State Health Technology Authority have enough confidence in its economic analysis to make a comparative effectiveness decision?

Washington HTA DES vs. BMS

Society for Cardiovascular Angiography and Interventions

Robert Bersin, MD FSCAI

SCAI Concerns

- Inappropriate clinical endpoints of mortality and MI have been used
- Heavy reliance on meta analyses and prior HTAs
- Lack of inclusion of other more contemporary data
- Potential of a double standard with respect to the availability of DES to the citizens of Washington

Inappropriate Clinical Endpoint

- The pivotal trials comparing DES to BMS have either used some measure of restenosis or a combined endpoint and have not been powered to determine a mortality benefit
- Meta analyses primarily use data from the pivotal trials which were not powered for mortality, varied to some degree and generally used less complex patient and lesion subsets than what is seen in routine clinical practice
- Mortality is generally an inappropriate endpoint when dealing with a chronic disease and a therapy (stenting) that impacts only one aspect (angina) of the disease at a single time point in the disease process
- The emphasis on death, stent thrombosis and MI used in the meta analyses was an attempt to make sure that DES was not harming patients and was driven by concern over stent thrombosis with DES and not to show superiority of DES compared to BMS.

Heavy Reliance on Meta Analyses and other HTAs

- The heavy use of prior HTAs that reproduce older data sets to make current decisions is concerning in a field that is adding evidence almost daily
- We believe well designed published registries are the only way to assess some of the more complex ("real world") patient subsets

Contemporary Data

- While we understand the need to have some control over the data used in the HTA the lack of inclusion of very recent studies on mortality and DES seems an important limitation
- If you want to use mortality as a primary endpoint then you should consider more contemporary data in the analysis

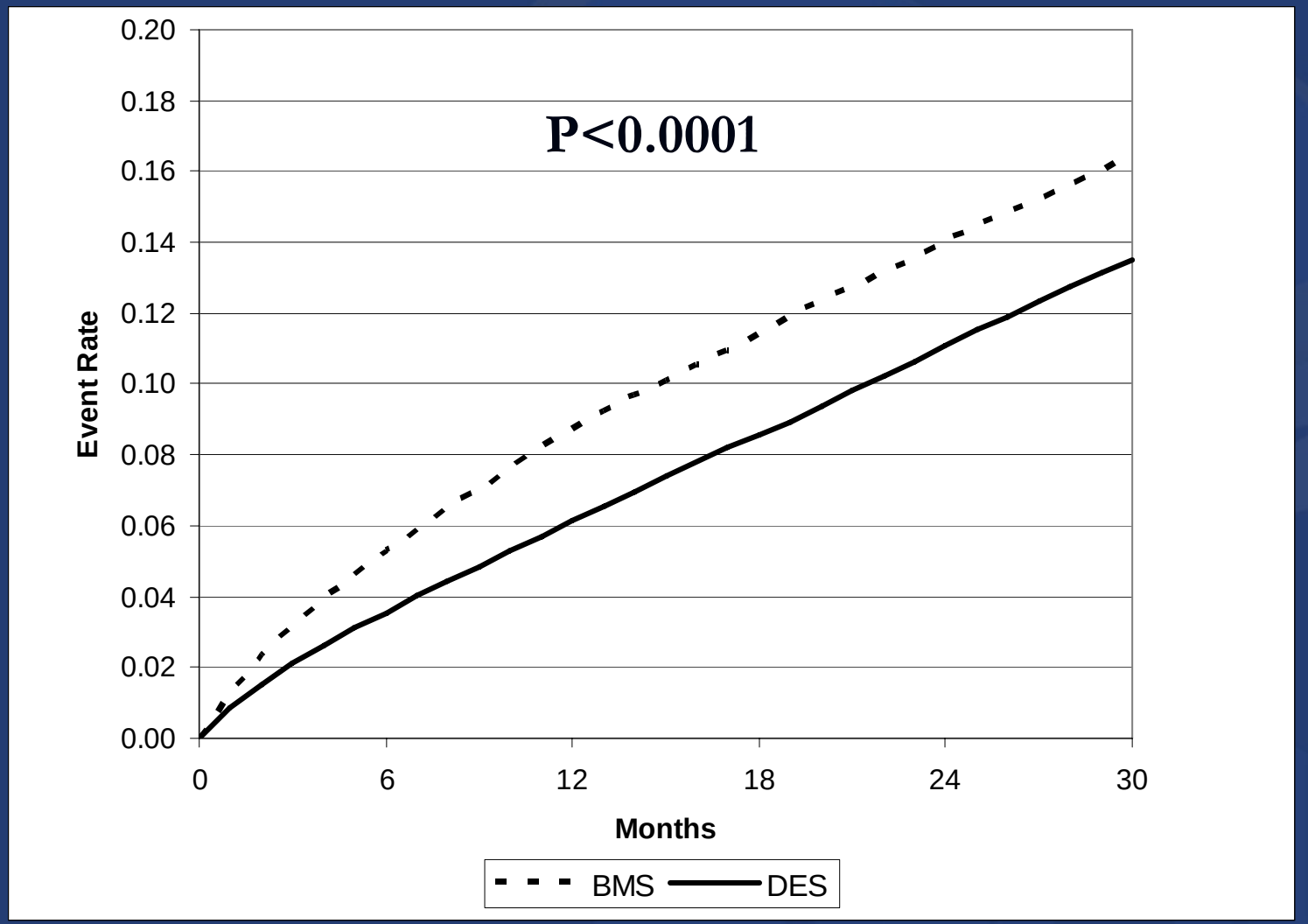
Outcomes Following Coronary Stenting:

A National Study of Long Term, Real-World Outcomes of Bare-Metal and Drug-Eluting Stents

N = 262,700 patients

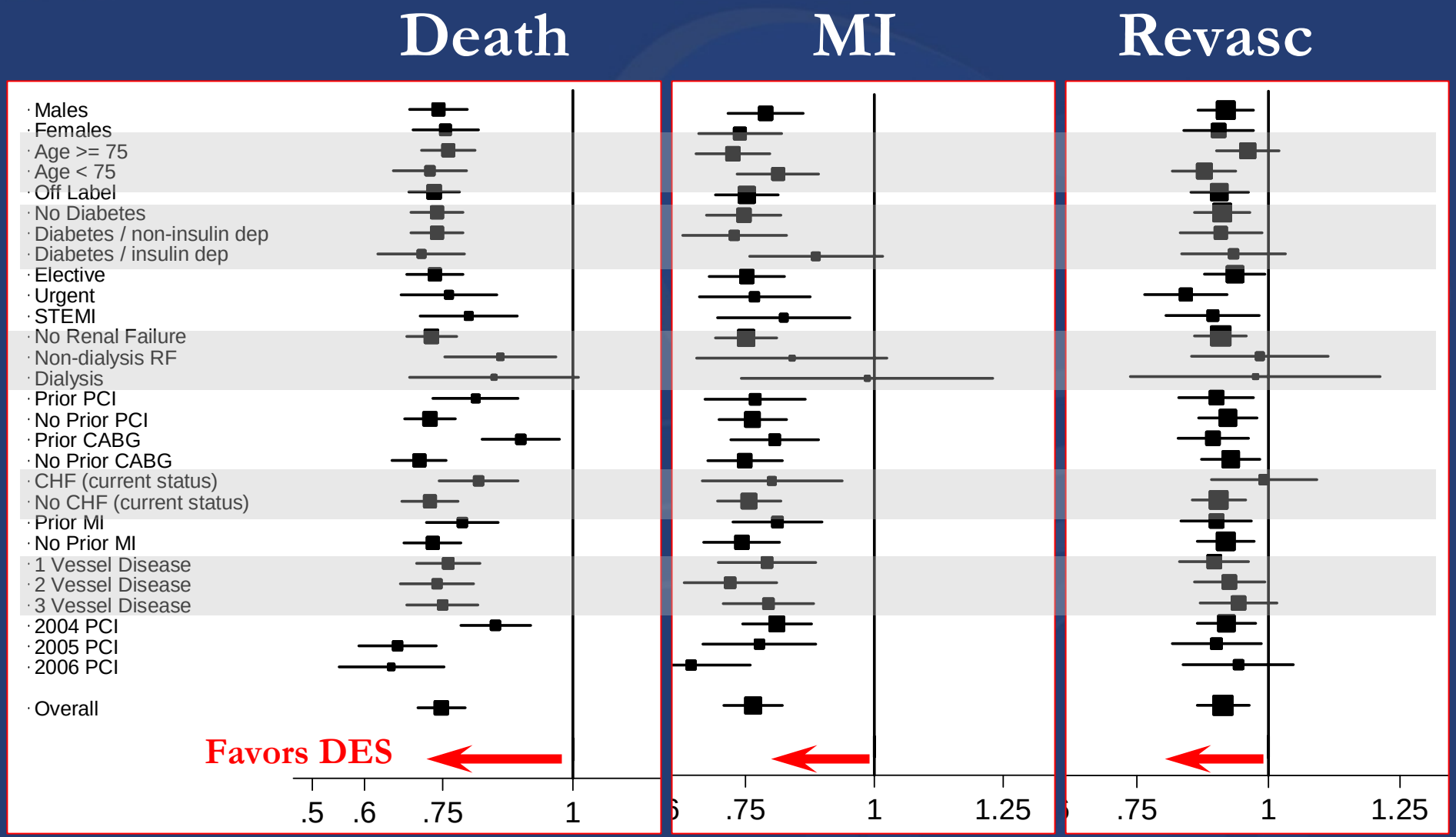
Douglas, P. S. et al. J Am Coll Cardiol 2009;53:1629-1641

Landmark Display: Mortality
N = 262,700



Douglas, P. S. et al. J Am Coll Cardiol 2009;53:1629-1641

Subgroup Analyses

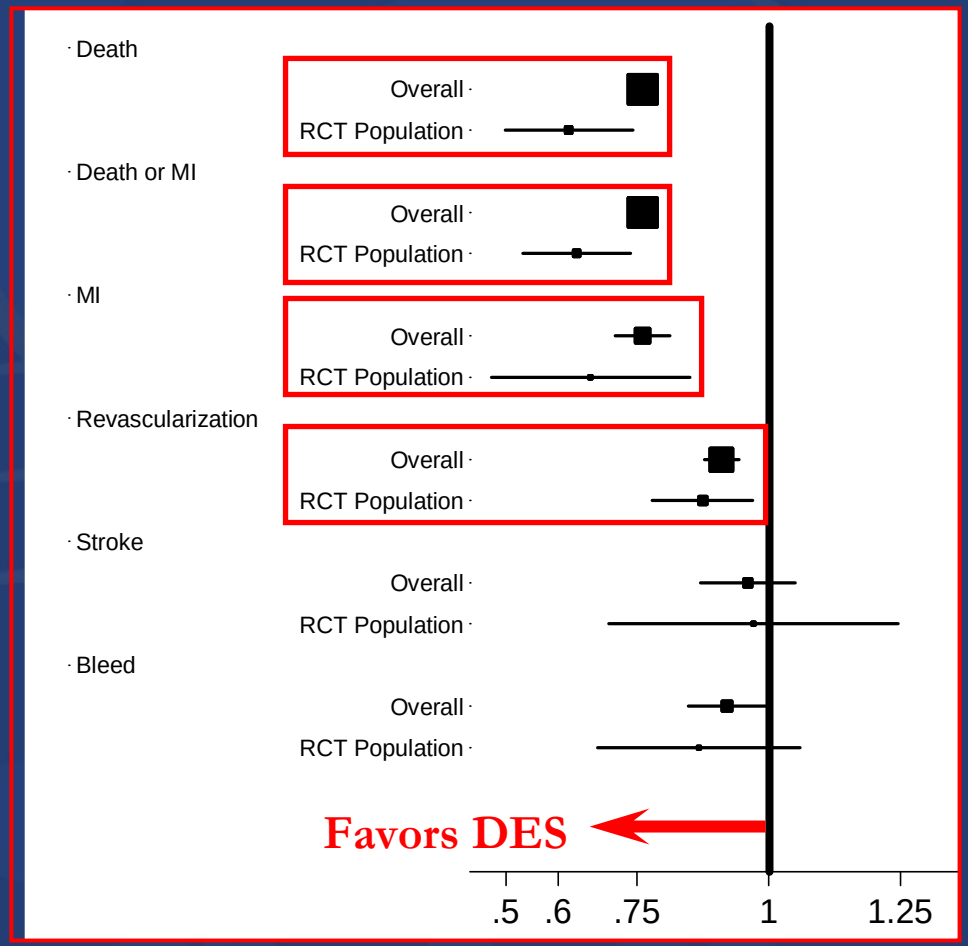


p<0.0001 p<0.0001 P=0.007

Douglas, P. S. et al. J Am Coll Cardiol 2009;53:1629-1641

Sensitivity Analysis: Patient Selection

- RCT - like population
- N = 49,355 (19%)
- 'Inclusion' criteria
  - Elective PCI, ≤ 2 stents
  - Native vessel, de novo
  - Class A or B lesions
  - Lesion length, diameter
  - ASA, clopidogrel OK
  - No CKD



Douglas, P. S. et al. J Am Coll Cardiol 2009;53:1629-1641

SCAI Recommendations and Comments

- We believe that DES should be allowed to be used in the appropriate patient as determined by the physician based on the unique patient, lesion and clinical characteristics as well as the filter of the most recent evidence
- We believe that DES is the standard of care for the majority of patients and using BMS instead will not yield the same results based on current evidence of superior DES outcomes
- It is important to remember that our only "skin" in this is the delivery of the best care that we know of to our patients

Abbott Vascular
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April 29, 2009

Ms. Leah Hole-Curry, JD
Program Director
Health Technology Assessment Program
Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

Dear Ms. Hole-Curry:

Abbott Vascular appreciates the opportunity to provide comments to the members of the Clinical Committee in response to the ***Cardiac Stents: Comparison of Drug Eluting Stents (DES) with Bare Metal Stents (BMS) Final Report*** posted on April 10, 2009.

Abbott Vascular, a Division of Abbott, is one of the world's leading vascular care businesses. The company is uniquely focused on transforming the treatment of vascular disease and improving patient care by combining the latest medical device innovations with world-class pharmaceuticals, investing in research and development and advancing medicine through training and education. As the market leader in bare metal stents (BMS) with the leading platform for drug eluting stents (DES), Abbott Vascular shares your commitment to optimizing health outcomes by making available advances in technology that improve the quality of life for residents in Washington State.

Below you will find our comments and recommendations.

SUMMARY OF COMMENTS AND RECOMMENDATIONS

I. EFFICACY OF DES

First Generation vs. Second Generation Drug Eluting Stents (DES)
The rapid market adoption of XIENCE V® (a second generation DES approved by the FDA in July 2008), reflects a significant change in clinical practice and physician preference. As such, we believe it is important to include results from clinical trials using XIENCE V® as part of the overall effort to evaluate the data on coronary stenting procedures.

In the SPIRIT II and III randomized controlled trials (RCT), XIENCE V® demonstrated superiority in late loss as well as clinically relevant reductions in target lesion revascularization (TLR), cardiac death and myocardial infarction (MI) versus TAXUS©

EXPRESS[2]. Since patient demographics in SPIRIT II and III are similar to the RCTs referred to in the Washington Health Technology Assessment (HTA), and because XIENCE V® has lower event rates than TAXUS, then by extension, XIENCE V® will have an even greater reduction in death, MI and TLR rates than TAXUS when compared to bare metal stents (BMS). Therefore, given the compelling evidence of better clinical outcomes with this second generation drug eluting stent, we believe the SPIRIT II and III RCTs should be included in the Health Care Authority's comprehensive analysis of coronary stenting.

Unfortunately, by only using data from randomized controlled trials comparing DES to BMS, DES vs. DES trials (such as SPIRIT II and III) were not included as part of the Final Report. It is important to consider that comparing a bare metal stent to a second generation DES in an RCT would be scientifically irrelevant, clinically unwise and potentially unethical. Second generation DES trials (e.g., DES vs. DES) are designed to be scientifically relevant, clinically acceptable, ethical, and reflective of current standards of care. By excluding data from the DES vs. DES trials, the Final Report is not reflective of current clinical practice patterns.

Interestingly, some DES vs. DES trials were included as part of the HTA Final Report through the Stettler network analysis (page 58). However, it appears that DES vs. DES studies involving second generation stents were the only studies excluded, potentially limiting the generalizability of the results of the HTA and underestimating the efficacy of DES vs. BMS. Thus, even though the level of evidence is considered high, forthcoming evidence on the second generation of DES, such as the results of the SPIRIT IV trial (the largest DES vs. DES RCT to date with results expected in Q4 2009), could easily change the conclusions of the Assessment.

Therefore, we recommend that the evidence on the efficacy of second generation drug eluting stents (as determined by SPIRIT II and III and other head-to-head trials of first vs. second generation drug eluting stents) be thoroughly examined when making a determination of the efficacy of DES VS. BMS.

Efficacy Endpoint

To assess the primary efficacy benefits of drug eluting stents as compared to BMS purely based on all death and MI does not fully evaluate the stents' labeled indication of improving the coronary luminal diameter. To adequately assess efficacy, the endpoint should include all the clinical endpoints that indicate a reduction in coronary luminal diameter. The Academic Research Consortium[i] (ARC) agrees with this point of view and recommended a composite of cardiac death, MI and target lesion revascularization (TLR) to assess device efficacy.

Consequently, we recommend that the evidence on the efficacy be based on the composite endpoint of cardiac death, MI and TLR as recommended by the ARC.

II. Effectiveness of DES

There were omissions of timely and clinically relevant data in the Final Report. For example, the results of a peer-reviewed, comparative effectiveness study of BMS vs. DES funded by AHRQ (presented on March 28, 2009 at the American College of Cardiology Meeting) were not included. The study, an article in-press for publication in the *Journal of the American College of Cardiology*, evaluated 217,674 DES patients and 45,025 BMS patients treated in the United States. This is the largest and most relevant study to assess comparative effectiveness of DES vs. BMS. The adjusted hazard ratio (HR) rates for death and MI were 0.75 (0.73, 0.77) and 0.76 (0.72, 0.80), respectively. This indicates that there is a 25% reduction in death and MI rates at 30 months post procedure for patients treated with DES. This data is particularly significant as it is reflective of real-world clinical experience.

Additionally, Doctors Ajay Kirtane and Gregg Stone performed a "Mega" meta-analysis of the RCTs and real-world registries, and reported on this analysis at the Transcatheter Cardiovascular Therapeutics (TCT) conference on October 13, 2008. This analysis is now an in-press article in *Circulation,* and showed that adjusted HR rates for the real-world registries for death and MI were 0.78 (0.71, 0.86) and 0.87 (0.78,0.97), respectively. These results are similar to those shown in the AHRQ analysis mentioned above.

As noted in the detailed section below, the Final Report also fails to consider a number of other recent real-world studies on the effectiveness of drug eluting stents vs. bare metal stents. Therefore, we recommend that the Clinical Committee carefully consider all of this additional evidence before making any decisions that potentially limit patient access to innovative technologies.

III. Safety of DES

As mentioned above in the Effectiveness section above, both the AHRQ-sponsored study and the "Mega" meta-analysis from Doctors Kirtane and Stone were excluded in the Final Report. We recommend that the Clinical Committee consider this additional evidence before making any final decisions.

IV. Cost-effectiveness

The HTA Final Report draws heavily on cost-effectiveness studies performed in countries other than the United States. The HTA concluded that inconsistency and variability

among the studies made it difficult to draw a definitive conclusion. However, the economic analyses done in the United States - rather than showing inconsistency across studies - demonstrate consistent economic benefits of DES stents as compared to BMS (page 147 in the Final Report). Therefore, we believe the Assessment should emphasize the consistency of results of the US studies demonstrating that DES is cost-effective, and that the Clinical Committee consider the difficulties associated with drawing conclusions for the cost-effectiveness of DES in Washington State based on non-US studies.

POLICY RECOMMENDATION

Based on the evidence of the efficacy, effectiveness and safety of DES, we recommend that the HTA include a policy recommendation that drug eluting stents should be made available to beneficiaries in the Washington State healthcare insurance programs without restriction. Additionally, the Clinical Committee may want to exercise its right to create an ad hoc Advisory Board to review this newest data before issuing any guidance on coronary stenting.

DETAILED COMMENTS

I. EFFICACY OF DES

Abbott Vascular submitted information to the Health Care Authority in Washington in June 2008 and again in January 2009 regarding several on-going clinical trials involving the use of our recently FDA-approved drug eluting stent, XIENCE V® Everolimus Eluting Coronary Stent System (XIENCE V® EECSS or simply XIENCE V®) often referred to as a second generation stent system. With specific trial activity looking at the efficacy in women, diabetics and other patient populations, we believe the results from these clinical trials will offer invaluable insight into the safety, utility and deliverability of the *second* generation of drug eluting stents.

The inclusion of XIENCE V® data in the HTA's evaluation of coronary stenting is important because of its timeliness and clinical relevance. The rapid market adoption of XIENCE V® (approved by the FDA in July 2008), reflects *a significant change in clinical practice and physician preference*. Failure to include evidence on newer or second generation DES in the Assessment results in an underestimation of the efficacy of DES vs. BMS.

The next few sections will elaborate on the evidence available that demonstrates that unique design features of the XIENCE V® stent lead to significantly better patient

outcomes. We also include information on the ongoing XIENCE V® clinical trials that will result in additional valuable evidence on the clinical benefits of DES vs. BMS.

Stent Design

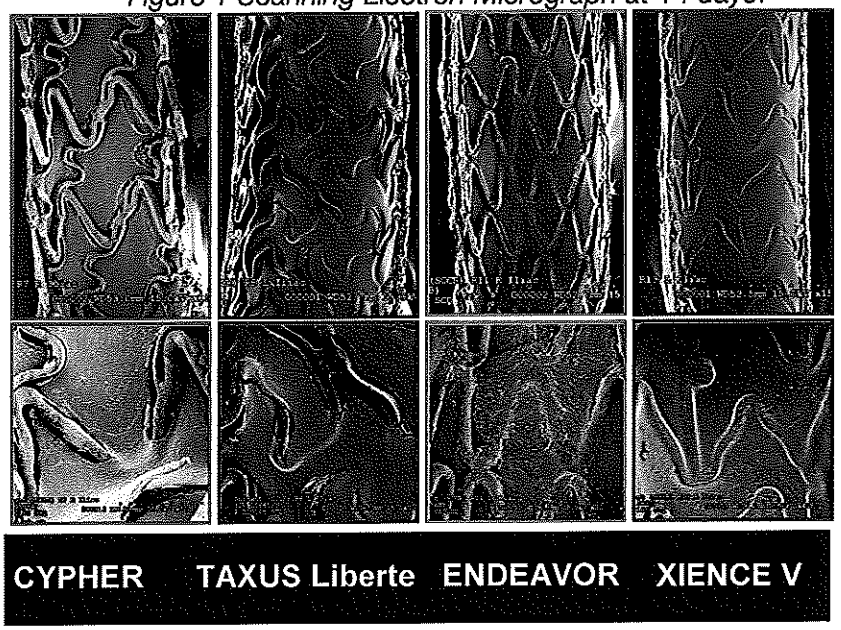
In a landmark study conducted by Simon et al[iii], endothelial coverage was shown to be highly dependent on the thickness of the stent implant; the thinner the strut the better the coverage. These results have been confirmed in clinical trials[iii,iv,v] that demonstrated that thinner struts are associated with reduced arterial injury and restenosis. XIENCE V® was specifically designed to minimize strut thickness in comparison to the first generation drug eluting stents - CYPHER® and TAXUS Express[2].

In the placement of a stent in a lesion, the permanent addition of bulk to the arterial wall must be considered. Stainless steel stents such as CYPHER® and TAXUS® implant approximately 150µm to the arterial wall. In the event of overlap that figure would double to approximately 300 µm. In addition, the dose of drug eluted at the point of overlap would also double. With increased bulk and increased elution of drug, focal exposure may lead to lack of endothelialization. One can only speculate on the consequences of increased bulk and exposure. However, from a purely geometric argument, a flexible thin-strutted stent with a lower dose of a limus-based drug would provide the least bulk associated with the effective delivery of a drug.

Pre-Clinical Studies

In publications of preclinical studies conducted by Finn et al[vi], the authors emphasize that drug choice and release kinetics affect arterial healing. In preclinical models, XIENCE V® has greater endothelial coverage after implantation in comparison with TAXUS®. In a recent publication from Dr. Virmani's group at CV Path[vii], endothelial cell recovery rates in drug eluting stents and bare metal stents were compared in a rabbit model. The study was designed to assess the impact of stent implantation on endothelial recovery and compared a thin-strutted bare metal stent (strut thickness = 81µm) with a variety of drug eluting stents. The drug eluting stents were XIENCE V® (strut/polymer thickness = 89µm), ENDEAVOR® (strut/polymer thickness = 96µm), TAXUS® Liberté™ (strut/polymer thickness = 113µm), and CYPHER® (strut/polymer thickness = 153µm). At 14 days, XIENCE V® had significantly more endothelial coverage on the struts than the other drug eluting stents evaluated. In addition, XIENCE V® had the fewest uncovered struts among the drug eluting stents. Figure 1 shows the scanning electron micrograph at 14 days.

Figure 1 Scanning Electron Micrograph at 14 days.



Clinical Evidence from US Approval Trial – SPIRIT III

US approval of the XIENCE V® stent was based on the data from three randomized trials. All three of these clinical trials (SPIRIT FIRST, SPIRIT II and SPIRIT III) have met their primary and major secondary endpoints with no adverse safety signals to date. The SPIRIT FIRST trial was the first clinical evaluation of the XIENCE V® EECSS and demonstrated both the short-term and long-term clinical safety of XIENCE V® in the treatment of subjects with single, *de novo* target lesions.

The SPIRIT III RCT included1,002 subjects (669 subjects in the XIENCE V® arm and 333 subjects in the TAXUS® arm). XIENCE V® demonstrated superiority to TAXUS® for the angiographic primary endpoint of in-segment late loss at 8 months ($P_{superiority}$ = 0.004). A post hoc analysis showed the reduction was consistent across several key subgroups including: age, gender, diabetic status, vessel size, and dual vessel treatment.

Additionally, SPIRIT III met its clinical primary endpoint of target vessel failure (TVF) at 9 months. The safety and efficacy of the XIENCE V® EECSS was sustained through the one year follow-up. A 24% reduction in TVF rates was observed at one-year in the XIENCE V® arm compared to the TAXUS® arm.

For the key secondary endpoint, MACE (composite of cardiac death, all MI and TLR), the rates were significantly lower at one-year in the XIENCE V® arm relative to the

TAXUS® arm (P=0.02). This reduction in MACE was consistent across all subgroups analyzed, with the exception of diabetic patients. [This apparent difference is driven by an unusual finding in which MACE rates in patients treated with TAXUS® are higher in non-diabetics than in diabetics. A resolution of this unlikely finding must await analyses in a larger sample size].

Summary of Current Clinical Evidence

The results of the SPIRIT III RCT at the two-year follow-up demonstrate that the safety and efficacy of XIENCE V® that were observed at one year[8] were sustained through two years[viii], as shown by the lower rates of TVF, MACE, and TLR in the XIENCE V® arm compared to the TAXUS® arm (see attached document from the January 26, 2009 edition of *Circulation*). Between 1 and 2 years, fewer MIs and very late stent thrombosis events were reported in XIENCE V® patients as compared to TAXUS® patients. This encouraging trend was strongly observed in patients that discontinued Thienopyridine for the first time between 6 months and two years. In this particular subset of patients, TAXUS® usage was associated with a greater rate of subsequent stent thrombosis than XIENCE V® usage (2.6% versus 0.4%, P=0.10). Finally, results from the subgroup analysis were generally consistent with overall study results at 1 year.

We suggest that the evidence provided differentiates the XIENCE V® EECSS from first generation stents. In particular, the stent design and the thin strut technology of XIENCE V® - as well as the evidence from pre-clinical studies - demonstrates more complete endothelialization with XIENCE V® compared to first generation drug eluting stents. In summary, the clinical evidence demonstrates more favorable long-term outcomes with XIENCE V® in comparison with the first generation TAXUS® stent in the SPIRIT III pivotal trial.

Ongoing XIENCE V® Clinical Trials

In addition to the data from the SPIRIT III pivotal trial, SPIRIT IV, the largest XIENCE V® vs. TAXUS® randomized controlled clinical trial to date (N=3,600), will reach its primary endpoint in the second half of 2009 and we expect to present the results in Q4, 2009 (More information about this trial may be obtained by sending an email to: medicalinformation@av.abbott.com).

Abbott Vascular believes that this additional information will provide the robust evidence needed for the Clinical Committee to come to a definitive conclusion on the clinical benefits of DES vs. BMS. However, in response to Abbott Vascular's similar comments and recommendations made to the Washington State HTA team on the Draft Report, the Washington State HTA group stated that only BMS vs. DES studies would be considered. In examining the Washington State HTA, we note that the results from the

Stettler network analysis were included as part of its Assessment. This meta-analysis included DES vs. DES studies which Washington State HTA noted provides valuable information in the Assessment of DES vs. BMS. It appears that DES vs. DES studies that involved second generation stents were the only studies excluded, potentially limiting the generalizability of the results of the HTA to both first and second generation DES. Therefore, we recommend that Washington State HTA team and the committee consider the results from the DES vs. DES studies for second generation stents before making its decision.

II. Effectiveness of DES

As previously mentioned, there were omissions of timely and clinically relevant data in the Final Report. The two most important studies are 1) the peer-reviewed, comparative effectiveness study of BMS vs. DES funded by AHRQ that was presented at on March 28, 2009 at the American College of Cardiology Meeting, and 2) the "mega"-meta analysis prepared by Doctors Kirtane and Stone that was presented on October 13, 2008 at the Transcatheter Cardiovascular Therapeutics (TCT) meeting.

1) The AHRQ-sponsored study, an article in-press for publication in the *Journal of the American College of Cardiology*, evaluated 217,674 DES patients and 45,025 BMS patients treated in the United States. This is the largest and most relevant study to assess comparative effectiveness of DES vs. BMS. The adjusted HR rates for death and MI were 0.75 (0.73, 0.77) and 0.76 (0.72, 0.80), respectively indicating a 25% reduction in death and MI rates at 30 months post procedure for patients treated with DES. Lower death and MI rates were also shown in key subgroups: gender, off label, diabetes, STEMI, prior PCI, Chronic Heart Failure, and multi-vessel disease. The study's conclusions include the following:

- No major DES safety concerns
- Lower death and MI rates in DES patients
- Slightly lower TLR revascularization, bleeding rates
- Similar stroke rates

2) The Kirtane and Stone "Mega"-meta analysis study evaluated 182,901 patients from registries. This is the largest meta-analysis to date that assesses comparative effectiveness of DES vs. BMS. Based on the random effects model, similar to the one used in Stettler's meta analysis, the analysis showed that the HR rates for death and myocardial infarction (MI) were 0.78 (0.71, 0.86) and 0.87 (0.78,0.97), respectively. This indicates that there is 22% reduction in death and13% reduction in MI rates at an average follow-up of 30 months for patients treated with DES. These results are similar to the AHRQ study even though there is very limited overlap between the two data sets. This analysis is an article in-press and is expected to be published in *Circulation* soon.

In addition, listed below are several real world registries whose results have been published in peer reviewed journals that were not included in the Assessment:

- S.T.E.N.T. registry: Catheterization and Cardiovascular Interventions 72:893–900 (2008)
- REWARDS registry: Am J Cardiol 2008;102:292–297
- EVENT registry: Catheter Cardiol Interv, Published Online: 9 Dec 2008
- ACC-NCDR CathPCI registry: AJC, February 2008;101: 286-292.
- ARRIVE I Catheter Cardiovasc Interv. 2008 Oct 1;72(4):433-45

These and other registries are representative of current practice patterns and provide important additional evidence on the effectiveness of drug eluting stents and should be included in the Assessment of cardiac stents.

Once the above data is included, overall we believe that the body of evidence on the effectiveness of DES vs. BMS represents a moderate level of evidence allowing conclusions to be drawn. Accordingly we recommend that the assessed level of evidence be changed from low to moderate.

III. Cost-Effectiveness

Abbott Vascular agrees with the HTA that comparing results from one health technology assessment to another can be difficult since health status, medical practices, health systems (and therefore the cost of treatment) are different from one country to another. As stated in an article by BG. Firth, L. Cooper and S. Ream[ix], there are pitfalls in using incremental cost-effectiveness ratios (ICER) using drug eluting stents as a case study. The pitfalls identified were:

- **Establishing the correct denominator for the cost-effectiveness ratio.** The primary objective associated improving quality of life is assumed to be relief of limiting angina, and the only utility score applied in the cost-effectiveness analysis (CEA) is a single estimate of time free of angina. Given the results of the AHRQ comparative effectiveness study showing a reduction in death and MI for DES as compared to BMS, one should consider what effect death and MI could have on cost-effectiveness rather than the avoidance of angina.
- **Establishing the correct numerator for the cost-effectiveness ratio.** Costs associated with medical devices are more dynamic than with pharmaceuticals. The costs of the new and the old technology are not independent but rather interdependent. In addition, there is a learning curve in terms of patient selection and use of the technology over time. The reality is that for a given technology, repeated application of this methodology at

different points in time may yield different conclusions for one or more of the reasons discussed above.

The article concludes "It is clearly important to appreciate that CEA used in the context of rapidly evolving technology, such as medical devices, is fraught with challenges, especially when the confidence intervals around the input values are in dispute. This case study sounds a note of caution to countries considering similar methods of medical technology assessment as used by NICE and emphasizes the importance of taking a broader economic view before making major policy decisions."

The HTA Final Report supports the above cautionary statement by their conclusion (p. 18): "Until there is more agreement on efficacy and effectiveness measures and rates with DES versus BMS, there will continue to be great variability among cost-effectiveness studies due to variations in parameters used."

However, it was not clearly pointed out in the HTA that all the US cost-effectiveness studies comparing DES to BMS consistently favor the use of DES. Therefore, rather than focusing on the inconsistent results from all the world-wide cost-effectiveness studies, the report should focus on consistency of the results from the United States.

Additionally, given the rapidly changing nature of stenting technology, it would be useful to have more up-to-date information on the cost-effectiveness of coronary stents, such as the cost-effectiveness analysis that will be performed for the SPIRIT IV clinical trial which will be available in Q1, 2010.

When additional information is available, we suggest the following:

- Higher quality studies based on the QHES be considered
- Since the evaluation of the quality of cost-effectiveness studies are somewhat subjective, more than one health economist should evaluate the studies
- Greater weight should be given to those studies conducted in the US

CONCLUSION

In conclusion, Abbott Vascular appreciates the opportunity to provide you and the Clinical Committee with this information which we hope will be useful in the technology assessment of the safety, efficacy, effectiveness and health economic considerations of cardiac stents. We recommend that the Clinical Committee:

- Assess evidence on the efficacy of second generation stents.
- Acknowledge that forthcoming evidence on the second generation of DES could change the conclusion of the Assessment.

- Consider the evidence from a number of recent real world DES registries that demonstrate that DES is more effective than BMS and change the assessed level of evidence from low to moderate.
- Address the difficulties associated with drawing conclusions for the cost-effectiveness of DES in WA State based largely on non-US studies.
- Re-focus Assessment on high quality cost-effectiveness studies particularly those conducted in the US.

In addition to this letter, attached you will find the following:

- An article by Dr. Gregg W. Stone, Professor of Medicine at the Columbia University Medical Center and Chairman of the Cardiovascular Research Foundation (CRF) in New York. This article was published in JAMA (April 2008) with results from the SPIRIT III pivotal trial.
- An article by Dr. Gregg W. Stone, Professor of Medicine at the Columbia University Medical Center and Chairman of the Cardiovascular Research Foundation (CRF) in New York. This article was published in Circulation (January 2009) with 2 year results from the SPIRIT III pivotal trial.
- A PowerPoint presentation given by Dr. Stone last October at the Transcatheter Cardiovascular Therapeutics conference. This review highlights the two year results of a Pooled Meta-analysis from the SPIRIT II and III clinical trials.
- A brief overview of our SPIRIT family of trials using XIENCE V®.
- A copy of the IFU for XIENCE V®
- A copy of the MULTI-LINK VISION® IFU

Please do not hesitate to contact me if you have any comments or questions regarding this information.

Sincerely,

[redacted]

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Randomized Comparison of Everolimus-Eluting and Paclitaxel-Eluting Stents. Two-Year Clinical Follow-Up From the 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 Trial

Gregg W. Stone, Mark Midei, William Newman, Mark Sanz, James B. Hermiller, Jerome Williams, Naim Farhat, Ronald Caputo, Nicholas Xenopoulos, Robert Applegate, Paul Gordon, Roseann M. White, Krishnankutty Sudhir, Donald E. Cutlip, John L. Petersen and for the SPIRIT III Investigators

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Randomized Comparison of Everolimus-Eluting and Paclitaxel-Eluting Stents

Two-Year Clinical Follow-Up From the 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 Trial

Gregg W. Stone, MD; Mark Midei, MD; William Newman, MD; Mark Sanz, MD; James B. Hermiller, MD; Jerome Williams, MD; Naim Farhat, MD; Ronald Caputo, MD; Nicholas Xenopoulos, MD; Robert Applegate, MD; Paul Gordon, MD; Roseann M. White, MA; Krishnankutty Sudhir, MD, PhD; Donald E. Cutlip, MD; John L. Petersen, MD; for the SPIRIT III Investigators

Background—In the prospective randomized 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 trial, an everolimus-eluting stent (EES) compared with a widely used paclitaxel-eluting stent (PES) resulted in a statistically significant reduction in angiographic in-segment late loss at 8 months and noninferior rates of target vessel failure (cardiac death, myocardial infarction, or target vessel revascularization) at 1 year. The safety and efficacy of EES after 1 year have not been reported.

Methods and Results—A total of 1002 patients with up to 2 de novo native coronary artery lesions (reference vessel diameter, 2.5 to 3.75 mm; lesion length ≤28 mm) were randomized 2:1 to EES versus PES. Antiplatelet therapy consisted of aspirin indefinitely and a thienopyridine for ≥6 months. Between 1 and 2 years, patients treated with EES compared with PES tended to have fewer episodes of protocol-defined stent thrombosis (0.2% versus 1.0%; $P=0.10$) and myocardial infarctions (0.5% versus 1.7%; $P=0.12$), with similar rates of cardiac death (0.3% versus 0.3%; $P=1.0$) and target vessel revascularization (2.9% versus 3.0%; $P=1.0$). As a result, at the completion of the 2-year follow-up, treatment with EES compared with PES resulted in a significant 32% reduction in target vessel failure (10.7% versus 15.4%; hazard ratio, 0.68; 95% confidence interval, 0.48 to 0.98; $P=0.04$) and a 45% reduction in major adverse cardiac events (cardiac death, myocardial infarction, or target lesion revascularization; 7.3% versus 12.8%; hazard ratio, 0.55; 95% confidence interval, 0.36 to 0.83; $P=0.004$). Among the 360 patients who discontinued clopidogrel or ticlopidine after 6 months, stent thrombosis subsequently developed in 0.4% of EES patients versus 2.6% of PES patients ($P=0.10$).

Conclusions—Patients treated with EES rather than PES experienced significantly improved event-free survival at a 2-year follow-up in the SPIRIT III trial, with continued divergence of the hazard curves for target vessel failure and major adverse cardiac events between 1 and 2 years evident. The encouraging trends toward fewer stent thrombosis episodes after 6 months in EES-treated patients who discontinued a thienopyridine and after 1 year in all patients treated with EES rather than PES deserve further study. **(*Circulation*. 2009;119:680-686.)**

Key Words: angioplasty ■ restenosis ■ stents ■ thrombosis

Compared with bare metal stents, both polymer-based paclitaxel-eluting stents (PES) and sirolimus-eluting stents have been shown to significantly reduce angiographic restenosis and recurrent ischemia necessitating repeat percutaneous coronary intervention and coronary artery bypass graft surgery.[1–3] However, the rates of primary stent thrombosis (thrombosis attributable to the stent itself as opposed to events occurring after treatment of restenosis) are increased

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Clinical trial registration information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00180479.

The names of the investigators, institutions, and research organizations participating in the SPIRIT III Trial appear in the Appendix of Reference 5.

Guest Editor for this article was Eric R. Bates, MD.

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with both PES and sirolimus-eluting stents compared with their bare metal counterparts, a difference that emerges >1 year after stent implantation.[3] With the goal of further enhancing the safety and efficacy of DES, an everolimus-eluting stent (EES) has been designed in which the antiproliferative agent is released from a thin (7.8 μm), nonadhesive, durable, biocompatible fluoropolymer coated onto a low-profile (0.0032-in strut thickness), flexible cobalt chromium stent. In a 14-day rabbit iliac model, endothelialization over the stent struts was more rapid with the EES than with stents eluting sirolimus, zotarolimus, or paclitaxel.[4] Whether these experimental observations translate into improved safety in humans is unknown.

Editorial p ●●●
Clinical Perspective p 686

In the pivotal 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 trial, patients with noncomplex coronary artery disease were randomized to treatment with a widely used PES or the EES. Angiographic follow-up at 8 months demonstrated a significant reduction in the primary angiographic end point of in-segment late loss with the EES compared with the PES; at 1 year, EES was noninferior to PES for the coprimary clinical end point of target vessel failure (TVF) but resulted in a significant reduction in major adverse cardiac events (MACE).[5] Longer-term follow-up is required to determine whether these benefits are sustained and to assess the late safety profile of the EES. The present study reports the 2-year clinical outcomes from the SPIRIT III trial.

Methods

Protocol Entry Criteria and Randomization

The design of the SPIRIT III trial has previously been described.[5] In brief, SPIRIT III was a prospective, multicenter, randomized, single-blind, controlled clinical trial in which 1002 patients with either 1 or 2 de novo native coronary artery lesions (maximum, 1 lesion per epicardial coronary artery) were randomized in a 2:1 ratio to receive the EES (Xience V, Abbott Vascular, Santa Clara, Calif) or the PES (TAXUS EXPRESS2, Boston Scientific, Natick, Mass). Patients were enrolled who were ≥18 years of age with stable or unstable angina or inducible ischemia undergoing percutaneous coronary intervention. Major clinical exclusion criteria included percutaneous coronary intervention in the target vessel before or planned within 9 months after the index procedure or in a nontarget vessel within 90 days before or planned within 9 months afterward; acute or recent myocardial infarction (MI); left ventricular ejection fraction <30%; use of long-term anticoagulation, recent major bleed, hemorrhagic diathesis, or objection to blood transfusions; contraindications or allergy to any of the study medications, components of the study stents, or iodinated contrast that could not be premedicated; elective surgery planned within 9 months after the procedure necessitating discontinuation of the antiplatelet agent; platelet count <100 000 or >700 000 cells/mm^3, white blood cell count <3000 cells/mm^3, serum creatinine >2.5 mg/dL, dialysis, or liver disease; stroke or transient ischemic attack within 6 months; comorbid conditions limiting life expectancy to <1 year or that could affect protocol compliance; and participation in another investigational study that has not yet reached its primary end point. The study was approved by the institutional review board at each participating center, and consecutive eligible patients signed written informed consent.

By visual assessment, all study lesions had a diameter stenosis of ≥50% and <100%, with a reference vessel diameter of 2.5 to 3.75 mm and lesion length of ≤28 mm. Angiographic exclusion criteria included ostial or left main lesions; bifurcation lesions with the side branch either >50% stenosed or >2 mm in diameter or requiring predilatation; excessive proximal tortuosity, lesion angulation or calcification, or thrombus; lesion located within a bypass graft conduit; or the presence of lesions with >40% stenosis within the target vessel or a likelihood that additional percutaneous coronary intervention would be required within 9 months.

After confirmation of angiographic eligibility, telephone randomization was performed in randomly alternating blocks of 3 and 6 patients with an automated voice response system stratified by the presence of diabetes, planned dual-vessel treatment, and study site. Although the operators were by necessity unblinded during the stent implant procedure, the patient and staff involved in follow-up assessments remained blinded throughout the follow-up period, with a standardized follow-up interview script used to reduce bias. Protocol-specified angiographic follow-up was performed at 240±28 days in 436 patients as previously described.[5] Clinical follow-up was performed at 1 month, 6 months, 9 months, and 1 year and then yearly through 5 years.

Medication Administration and Clinical Follow-Up

Procedural anticoagulation was achieved with either unfractionated heparin or bivalirudin as per standard of care, with glycoprotein IIb/IIIa inhibitors used per operator discretion. Patients were administered ≥300 mg aspirin before catheterization. A ≥300-mg oral dose of clopidogrel was recommended before the procedure and was required in all cases within 1 hour after stent implantation. The protocol recommended use of aspirin ≥80 mg daily indefinitely and clopidogrel 75 mg daily for a minimum of 6 months; a longer duration of clopidogrel use was permitted at the discretion of the treating physicians. Other medications were prescribed as per standard of care. Clinical follow-up was scheduled at 30±7, 180±14, 240±28, 270±14, and 365±28 days and then yearly (±28 days) through 5 years.

Data Management

Independent study monitors verified 100% of case report form data onsite. An independent committee blinded to treatment allocation adjudicated all MACE after review of original source documentation. A second clinical events committee blinded to randomization performed a post hoc adjudication of stent thrombosis using the Academic Research Consortium (ARC) definitions.[6] Independent core angiographic and intravascular ultrasound laboratory analyses were performed by technicians blinded to treatment assignment and clinical outcomes using validated methods as previously described.[7,8] A Data Safety and Monitoring Committee periodically reviewed blinded safety data, each time recommending that the study continue without modification.

Clinical End Points and Definitions

The primary clinical end point of the SPIRIT III trial was TVF, consisting of the composite of cardiac death, MI, or ischemia-driven target vessel revascularization (TVR) by either percutaneous coronary intervention or bypass graft surgery. Secondary end points included MACE, defined as the composite of cardiac death, MI, or ischemia-driven target lesion revascularization (TLR), as well as the individual components of TVF and MACE and stent thrombosis. Target vessel (or lesion) revascularization was considered to be ischemia driven if associated with a positive functional study, a target vessel (or lesion) diameter stenosis ≥50% by core laboratory quantitative analysis with ischemic symptoms, or a target vessel (or lesion) diameter stenosis ≥70% with or without documented ischemia. MI was defined as either the development of new pathological Q waves ≥0.4 seconds in duration in ≥2 contiguous leads or an elevation of creatine phosphokinase levels to >2.0 times normal with positive creatine phosphokinase-MB. Stent thrombosis was prospectively defined by protocol as an acute coronary syndrome with angiographic evidence of thrombus within or adjacent to a previously treated target lesion or, in the absence of angiography, any unexplained death or acute MI with ST-segment elevation or new Q waves in the

Table 1. Baseline Characteristics and Antiplatelet Medication Use

	EES (n=669 patients)	PES (n=332 patients)
Clinical features		
Age, y	63.2±10.5	62.8±10.2
Male, n (%)	469/669 (70.1)	218/332 (65.7)
Diabetes mellitus, n (%)	198/669 (29.6)	92/330 (27.9)
Insulin requiring	52/669 (7.8)	18/330 (5.5)
Hypertension, n (%)	510/669 (76.2)	245/331 (74.0)
Hypercholesterolemia, n (%)	489/659 (74.2)	233/326 (71.5)
Current smoker, n (%)	154/659 (23.4)	73/324 (22.5)
Prior MI, n (%)	130/652 (19.9)	59/327 (18.0)
Unstable angina, n (%)	123/657 (18.7)	82/327 (25.1)
Lesions treated, n	1.2±0.4	1.2±0.4
Target vessels, n (%)	772	383
Left anterior descending	317/768 (41.3)	164/382 (42.9)
Left circumflex	212/768 (27.6)	108/382 (28.3)
Right	238/768 (31.0)	109/382 (28.5)
Left main (protected)	1/768 (0.1)	1/382 (0.3)
Target lesion, n	772	383
Reference vessel diameter, mm	2.77±0.45	2.76±0.46
Minimal luminal diameter, mm	0.82±0.41	0.83±0.40
Diameter stenosis, %	70.0±13.3	69.4±13.6
Lesion length, mm	14.7±5.6	14.7±5.7
Aspirin use, n (%)		
At 6 mo	645/662 (97.4)	316/325 (97.2)
At 1 y	630/647 (97.4)	305/314 (97.1)
At 2 y	602/626 (96.2)	285/299 (95.3)
Thienopyridine use, n (%)		
At 6 mo	628/663 (94.7)	307/325 (94.5)
At 1 y	464/647 (71.7)	225/314 (71.7)
At 2 y	372/626 (59.4)	191/299 (63.9)

Values are expressed as mean±SD where appropriate.

distribution of the target lesion occurring within 30 days after the procedure. Definite or probable stent thrombosis also was adjudicated in a post hoc analysis with the ARC definitions.[6]

Statistical Methods

Categorical variables were compared by the Fisher exact test. Continuous variables are presented as mean±SD and were compared by *t* test. All analyses are by intention to treat using all patients randomized in the study, regardless of the treatment actually received. However, patients lost to follow-up in whom no event had occurred before the follow-up windows were not included in the denominator for calculations of binary end points. Time-to-event hazard curves also were constructed with Kaplan–Meier estimates and compared by log-rank test. A 2-sided value of $\alpha=0.05$ was used for all statistical tests to define significance. All statistical analyses were performed by SAS version 9.1.3 (SAS Institute, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients and Medications

A total of 1002 patients were enrolled at 75 US sites in the SPIRIT III trial between June 22, 2005, and March 15, 2006, and were randomized to receive EES (n=669) or PES (n=333). Baseline clinical and angiographic characteristics were well matched between the groups (Table 1). As also shown in Table 1, aspirin use was high in both groups throughout the 2-year study period, whereas thienopyridine use declined progressively over time, so that 60.9% of patients were taking either clopidogrel or ticlopidine at the end of 2 years.

Table 2. Clinical Outcomes at 2 Years

	EES (n=642 patients), n (%)	PES (n=309 patients), n (%)	*P*
All-cause death	13 (2.0)	8 (2.6)	0.64
Cardiac death*	7 (1.1)	4 (1.3)	0.75
Noncardiac death	6 (0.9)	4 (1.3)	0.74
MI*	21/637 (3.3)	18/305 (5.9)	0.08
Q wave	3/637 (0.5)	2/305 (0.7)	0.66
Non–Q wave	18/637 (2.8)	16/305 (5.2)	0.09
All-cause death or MI	31 (4.8)	25 (8.1)	0.055
Cardiac death or MI*	26/637 (4.1)	21/305 (6.9)	0.08
TLR, all	39 (6.1)	35 (11.3)	0.006
Ischemia driven	29 (4.5)	23 (7.4)	0.07
Non–ischemia driven	11 (1.7)	17 (5.5)	0.002
TVR, remote, all	35 (5.5)	23 (7.4)	0.25
Ischemia driven	31 (4.8)	20 (6.5)	0.29
Non–ischemia driven	5 (0.8)	4 (1.3)	0.48
TVR, all	65 (10.1)	43 (13.9)	0.10
Ischemia driven	56 (8.7)	34 (11.0)	0.29
Non–ischemia driven	16 (2.5)	18 (5.8)	0.01
MACE*	49/637 (7.7)	42/305 (13.8)	0.005
TVF*	72/637 (11.3)	50/305 (16.4)	0.04

*As per the statistical analysis plan, because the composite TVF and MACE end points included cardiac deaths only, patients with noncardiac deaths were excluded from the denominator. MACE included cardiac death, MI, or ischemia-driven TLR. TVF included cardiac death, MI, or ischemia-driven TVR.

Clinical Outcomes at 2 Years

Clinical follow-up was available at 2 years in 951 patients (94.9%), including 642 EES patients and 309 PES patients. Table 2 reports the binomial rates of the major clinical end points at 2 years, and Figure 1 displays the Kaplan–Meier hazard event curves. At 1 year, no significant differences were found in the rates of TVF between the EES and PES groups (8.3% versus 10.8%; hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.48 to 1.10; $P=0.13$). As seen in Figure 1 and Table 3, however, between 1 and 2 years, TVF events occurred more frequently in the PES group than in the EES group, so that by the end of the 2-year follow-up period, treatment with EES compared with PES resulted in a significant 32% reduction in the rate of TVF (10.7% versus 15.4%; HR, 0.68; 95% CI, 0.48 to 0.98; $P=0.04$). As also seen in Figure 1 and Table 3, MACE occurred more frequently in PES- compared with EES-treated patients between 1 and 2

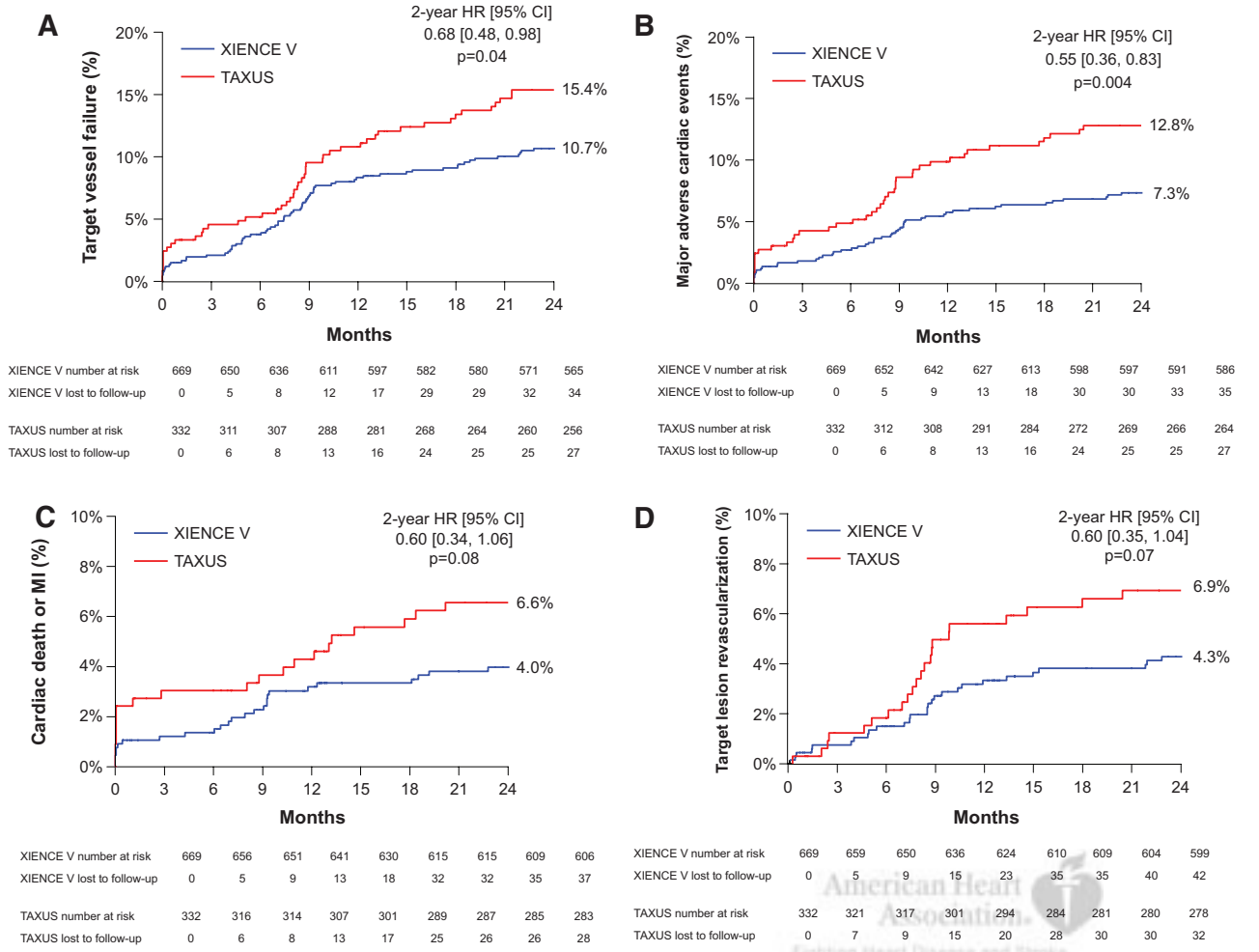

Figure 1. Time-to-event hazard curves to 2 years among patients randomized to EES or PES. Top left, Rates of TVF; top right, MACE; bottom left, cardiac death or MI; bottom right, TLR. Note that the graphs continue to 758 days, representing 2 years (730 days) plus the outside of the follow-up window of ±28 days.

years, so that by at the end of the 2-year follow-up period, patients treated with EES rather than PES had a significant 45% reduction in MACE (7.3% versus 12.8%; HR, 0.55; 95% CI, 0.36 to 0.83; $P=0.004$).

Between 1 and 2 years of follow-up, treatment with EES compared with PES resulted in a trend toward fewer MIs, with nonsignificantly different interval rates of all-cause death, cardiac death, TLR, and TVR (Table 3). The 2-year composite rate of cardiac death or MI thus tended to be reduced in patients treated with EES compared with PES as a result of fewer periprocedural MIs and the trend toward fewer late MIs with EES (Figure 1). A strong trend also was present toward a 40% reduction in the composite rate of all-cause death or MI in patients treated with EES compared with PES (4.8% versus 8.1%; relative risk [RR], 0.60; 95% CI, 0.36 to 0.99; $P=0.055$). As also seen in Figure 1, a trend was present toward less TLR at 2 years in patients treated with EES rather than PES (4.3% versus 6.9%; HR, 0.60; 95% CI, 0.35 to 1.04; $P=0.07$).

Stent Thrombosis

As seen in Table 4, at the end of the 2-year follow-up period, stent thrombosis according to the prespecified protocol definition occurred in 1.0% of EES patients and 1.7% of PES patients (RR, 0.58; 95% CI, 0.18 to 1.87; $P=0.35$). The protocol-defined rates of stent thrombosis were comparable between the 2 groups within 1 year of randomization, whereas stent thrombosis between 1 and 2 years occurred in 0.2% of EES patients and in 1.0% of PES patients (RR, 0.16; 95% CI, 0.02 to 1.53; $P=0.10$). Similar trends were present when the post hoc ARC definitions of definite or probable stent thrombosis were used (Table 4).

As shown in Figure 2, the 2-year rates of stent thrombosis according to the prespecified protocol definition were comparable among EES and PES patients who never discontinued a thienopyridine during the follow-up period (0.6% in both groups). In patients who discontinued clopidogrel or ticlopidine before 6 months, the rate of subsequent stent thrombosis after thienopyridine discontinuation through the end of the 2-year follow-up period was increased compared with patients who never discontinued a thienopyridine but similar in the EES and PES groups (2.8% and 2.9%, respectively). In contrast, among the 360 patients who discontinued clopidogrel or ticlopidine after 6 months and before 2 years, stent thrombosis subsequently developed after thienopyridine discontinuation in 1 of 244 EES patients (0.4%) and in 3 of 116 PES patients (2.6%; $P=0.10$; Figures 2 and 3).

Table 3. Adverse Events Occurring Between 1 and 2 Years of Follow-Up

	EES (n=628 patients), n (%)	PES (n=300 patients), n (%)	*P*
All-cause death	5 (0.8)	4 (1.3)	0.48
Cardiac	2 (0.3)	1 (0.3)	1.0
Noncardiac	3 (0.5)	3 (1.0)	0.40
MI	3 (0.5)	5 (1.7)	0.12
Q wave	1 (0.2)	1 (0.3)	0.54
Non–Q wave	2 (0.3)	4 (1.3)	0.09
TLR, all	10 (1.6)	5 (1.7)	1.0
Ischemia driven	9 (1.4)	5 (1.7)	0.78
Non–ischemia driven	1 (0.2)	0 (0.0)	1.0
TVR, remote, all	11 (1.7)	5 (1.7)	1.0
Ischemia driven	11 (1.7)	5 (1.7)	1.0
Non–ischemia driven	0 (0.0)	0 (0.0)	. . .
TVR, all	19 (3.0)	9 (3.0)	1.0
Ischemia driven	18 (2.9)	9 (3.0)	1.0
Non–ischemia driven	1 (0.2)	0 (0.0)	1.0
MACE	12 (1.9)	9 (3.0)	0.35
TVF	20 (3.2)	13 (4.3)	0.45

Discussion

In the pivotal prospective, randomized SPIRIT III trial, patients randomized to EES rather than PES experienced fewer periprocedural MIs and less angiographic late loss at 8 months with fewer subsequent TLR procedures between 6 and 12 months, resulting in a significant reduction in MACE and noninferior rates of TVF with the EES at 9 months and 1 year.[5] The present report demonstrates that between 1 and 2 years of follow-up after stent implantation, the advantages of the EES compared with the PES continue to accrue, with fewer episodes of very late stent thrombosis and MI occurring in patients having received the EES. As a result, the hazard curves for TVF and MACE between 1 and 2 years continued to diverge, so that at the end of the 2-year follow-up period, patients treated with the EES rather than PES had a significant 32% reduction in the rate of the primary clinical end point of TVF (10.7% versus 15.4%; HR, 0.68; 95% CI, 0.48 to 0.98; $P=0.04$) and a 45% reduction in MACE (7.3% versus 12.8%; HR, 0.55; 95% CI, 0.36 to 0.83; $P=0.004$),

Table 4. Stent Thrombosis Rates According to the Prespecified Protocol Definition and the Posthoc ARC Definitions

	EES, n/N (%)	PES, n/N (%)	*P*
Protocol definition, all	6/627 (1.0)	5/301 (1.7)	0.35
Early (up to 30 d)	3/667 (0.4)	0/330 (0)	0.55
Late (31 d–1 y)	2/647 (0.3)	2/315 (0.6)	0.60
Very late (>1–2 y)	1/626 (0.2)	3/300 (1.0)	0.10
ARC definite or probable, all	8/629 (1.3)	5/300 (1.7)	0.77
Early (up to 30 d)	3/667 (0.4)	0/330 (0)	0.55
Late (31 d–1 y)	3/648 (0.5)	2/315 (0.6)	0.66
Very late (>1–2 y)	2/627 (0.3)	3/299 (1.0)	0.34
ARC definite, all	6/629 (1.0)	2/300 (0.7)	1.00
ARC probable, all	2/629 (0.3)	3/300 (1.0)	0.34

All the stent thrombosis episodes were "primary" stent thromboses attributable to the original stent implanted (ie, none occurred subsequent to revascularization procedures).

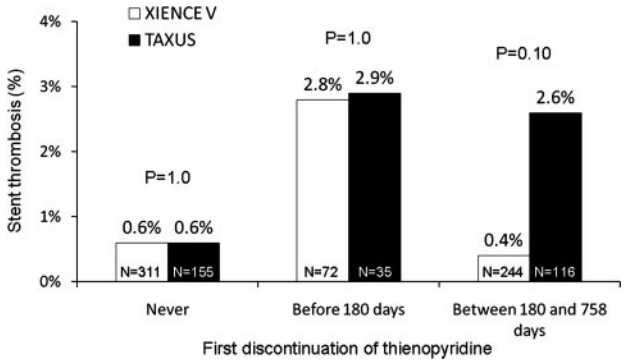

Figure 2. Incidence of the prespecified protocol-defined stent thrombosis in patients randomized to EES or PES who never discontinued a thienopyridine (clopidogrel or ticlopidine) during the 2-year study period (left) and the subsequent rates of stent thrombosis in patients who discontinued a thienopyridine before 6 months (middle) and at any time after 6 months (right).

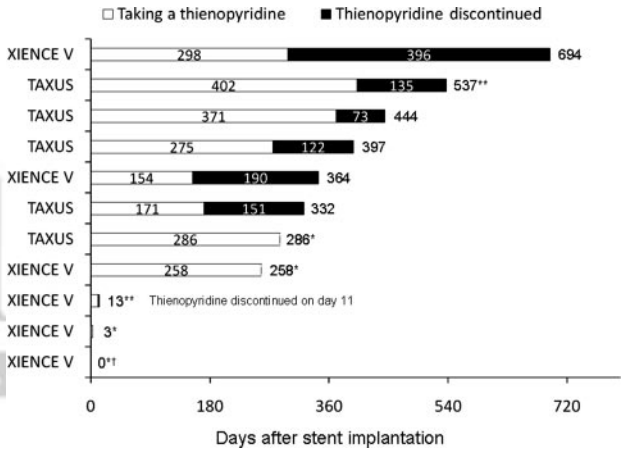

Figure 3. Relationship between the timing of thienopyridine discontinuation and protocol-defined stent thrombosis in individual patients. The number on the right of each bar is the day after device implantation on which stent thrombosis occurred. Stent thrombosis within 2 years occurred in 5 patients who were actively taking clopidogrel (in 1 patient, aspirin had been discontinued) and in 6 patients after thienopyridine discontinuation (including 1 patient in whom aspirin had been discontinued). None of the patients who discontinued the thienopyridine and subsequently developed stent thrombosis had restarted the thienopyridine before the thrombotic event. See text for detailed discussion of intragroup rates. Note that the sample size in the EES group is twice that in the PES group (2:1 randomization); thus, the number of individual patients represented with each stent type does not directly reflect the group event rates. *Patients in whom stent thrombosis occurred who were actively taking a thienopyridine. **The 2 patients in whom aspirin had been discontinued before stent thrombosis. †One patient who developed acute stent thrombosis (on day 0) in whom clopidogrel was subsequently discontinued on day 178 (and in whom stent thrombosis did not thereafter occur).

attributable to fewer MIs and less recurrent ischemia necessitating repeat TLR procedures through 2 years.

The present results with the EES are consistent with the clinical results from the smaller SPIRIT II trial, in which 300 patients in Europe and Asia Pacific were randomized 3:1 to EES versus PES.[9] At the 2-year follow-up in SPIRIT II, treatment with EES compared with PES was associated with a nonsignificant 40% reduction in MACE (6.6% versus 11.0%; $P=0.31$), similar to the significant 45% reduction present in the larger SPIRIT III trial.[10] Of potential concern in SPIRIT II, however, was the observation that among 97 EES patients who underwent routine follow-up angiography at both 6 months and 2 years, in-stent late loss significantly increased over time, whereas no such incremental late loss was noted in 35 PES patients.[10] However, in the larger SPIRIT III trial, in which angiographic follow-up beyond 1 year was not performed, the absolute reduction in ischemia-driven TLR with the EES compared with PES present at 1 year was preserved at 2 years. Specifically, in SPIRIT III, ischemia-driven TLR was required between 1 and 2 years in 1.4% and 1.7% of EES and PES patients, respectively. This finding confirms and extends the results from SPIRIT II in which no late catch-up was evident in either the differences in in-segment binary restenosis or TLR between 6 and 24 months, both of which favored EES compared with PES. Thus, both SPIRIT studies have demonstrated that the early reduction in clinical restenosis (TLR) with EES compared with PES is sustained through 2 years, although longer-term follow-up is required to assess the late durability of the clinical advantages of the EES.

Use of both PES and sirolimus-eluting stents has been associated with increased rates of primary stent thrombosis compared with bare metal stents, a difference that emerges only after 1 year of follow-up.[3] In this regard, it is noteworthy that in the present randomized trial, the rates of stent thrombosis were comparable between the PES and EES within the first year after implantation; after 1 year, however, trends were present for fewer stent thrombosis episodes with the EES than with the PES when assessed by either the prespecified protocol definition (0.2% versus 1.0%, respectively) or the post hoc ARC definitions (0.3% versus 1.0%, respectively). Moreover, although numerous studies have demonstrated that premature clopidogrel discontinuation (within 6 months after stent implantation, the duration of dual antiplatelet therapy required in the protocol) is a major risk factor for stent thrombosis,[11,12] some[13] but not all[14] prior studies have found that prolonged thienopyridine administration (beyond 6 months) is protective against subsequent composite death or MI in sirolimus-eluting stent and PES patients. In the present study, thienopyridine discontinuation within the first 6 months was associated with a nearly 5-fold increase in the rates of thrombosis with both EES and PES, consistent with these earlier studies.[11,12] Thienopyridine discontinuation for the first time after 6 months, however, was associated with a greater rate of subsequent stent thrombosis with the PES than with the EES (2.6% versus 0.4%), although given the relatively low rates of stent thrombosis, this difference did not reach statistical significance ($P=0.10$). Moreover, the duration between thienopyridine discontinuation after 6 months and subsequent stent thrombosis in PES-treated patients ranged from 73 to 135 days; as such, no definite conclusions can be drawn as to whether late thienopyridine discontinuation was causally related to subsequent stent thrombosis in these patients or whether stent thrombosis might have been prevented if dual antiplatelet therapy had not been interrupted. Thus, although the trends toward fewer subsequent stent thrombosis episodes after 6 months in EES-treated patients who discontinued a thienopyridine and in all patients after 1 year treated with EES rather than PES are encouraging and consistent with the more rapid endothelialization expected with thin-strut stents[15] and with the EES in particular,[4] larger studies are required to confirm these observations.

In addition to the need for longer-term follow-up, other limitations of the SPIRIT III trial should be acknowledged. The events and their timing examined in the present analysis were secondary end points; thus, the findings should be considered hypothesis generating. Logistic considerations precluded blinding the operator to stent type, although the patients, follow-up study coordinators, and clinical events committee and core laboratory personnel were blinded and review of original source documents for clinical event adjudication was required. Routine angiographic follow-up was performed in 43.5% of patients at 8 months, potentially biasing subsequent clinical treatment decisions.[16] However, this would not be expected to affect event rates between 1 and 2 years as described in the present report. The duration of dual antiplatelet therapy was not randomized, so the analysis of stent thrombosis rates according to dual antiplatelet use should not be considered definitive. Approximately 5% of patients were lost to follow-up at 2 years, warranting additional caution in the interpretation of differences in low-frequency safety events. Finally, the results of the present trial cannot be extended to higher-risk patients and lesion types excluded from enrollment.

Conclusions

At the 2-year follow-up of the SPIRIT III trial, patients treated with EES rather than PES experienced significantly improved event-free survival, with statistically significant 32% and 45% reductions, respectively, in TVF and MACE as a result of fewer MIs and ischemic TLR procedures. The magnitude of the reduction in TLR with EES compared with PES at 1 year remains robust at 2 years, with no late catch-up apparent. The encouraging trends toward fewer subsequent stent thrombosis episodes after 6 months in EES-treated patients who discontinued a thienopyridine and in all patients after 1 year treated with EES rather than PES are potentially important and deserve further study.

Sources of Funding

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The sponsor was provided the opportunity for a nonbinding review of the manuscript before its submission.

Disclosures

Dr Stone reports having received research support from Abbott Vascular and Boston Scientific Corp and honoraria from Medtronic. Dr Hermiller reports serving as a consultant for Abbott Vascular and Boston Scientific Corp. Dr Applegate reports having received research support from Cordis and serving as a consultant for Abbott Vascular. Dr Gordon reports having received research support from Abbott Vascular and Boston Scientific Corp. Drs White and Sudhir are full-time employees of and own stock and/or options in Abbott Vascular. Dr Petersen reports having received research grants from Cordis Corp, Conor MedSystems, and Abbott Vascular. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Because >1 million drug-eluting stents are implanted each year in patients with coronary artery disease, the safety and efficacy of these devices continue to be of paramount importance. The 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 trial was a prospective, randomized trial that evaluated a second-generation everolimus-eluting stent (EES) compared with a widely used paclitaxel-eluting stent (PES) in 1002 patients at 75 US sites. At 2 years of follow-up, the EES compared with the PES resulted in a 32% reduction (10.7% versus 15.4%; $P=0.04$) in the composite safety and efficacy measure of target vessel failure (cardiac death, myocardial infarction, or recurrent ischemia necessitating target vessel revascularization with either repeat percutaneous coronary intervention or bypass graft surgery). Major adverse cardiac events (cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization) also were reduced by 45% (7.3% versus 12.8%; $P=0.004$) with the EES compared with the PES. The 2-year rates of all-cause death or myocardial infarction tended to be reduced with EES compared with PES (4.8% versus 8.1%; $P=0.055$). This favorable balance of safety and efficacy with the EES was driven by fewer episodes of early and late myocardial infarctions and fewer target lesion revascularization procedures required between 6 and 12 months. Between 1 and 2 years, there tended to be fewer stent thrombosis events with the EES compared with the PES, especially in patients who had discontinued clopidogrel after 6 months, which in part contributed to the improved outcomes. Larger studies are underway to further evaluate the encouraging trends toward less composite death or myocardial infarction and late stent thrombosis seen with the EES in the present study.

Comparison of an Everolimus-Eluting Stent and a Paclitaxel-Eluting Stent in Patients With Coronary Artery Disease: A Randomized Trial

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Comparison of an Everolimus-Eluting Stent and a Paclitaxel-Eluting Stent in Patients With Coronary Artery Disease

A Randomized Trial

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Context A thin, cobalt-chromium stent eluting the antiproliferative agent everolimus from a nonadhesive, durable fluoropolymer has shown promise in preliminary studies in improving clinical and angiographic outcomes in patients with coronary artery disease.

Objective To evaluate the safety and efficacy of an everolimus-eluting stent compared with a widely used paclitaxel-eluting stent.

Design, Setting, and Patients The SPIRIT III trial, a prospective, randomized, single-blind, controlled trial enrolling patients at 65 academic and community-based US institutions between June 22, 2005, and March 15, 2006. Patients were 1002 men and women undergoing percutaneous coronary intervention in lesions 28 mm or less in length and with reference vessel diameter between 2.5 and 3.75 mm. Angiographic follow-up was prespecified at 8 months in 564 patients and completed in 436 patients. Clinical follow-up was performed at 1, 6, 9, and 12 months.

Interventions Patients were randomized 2:1 to receive the everolimus-eluting stent (n=669) or the paclitaxel-eluting stent (n=333).

Main Outcome Measures The primary end point was noninferiority or superiority of angiographic in-segment late loss. The major secondary end point was noninferiority assessment of target vessel failure events (cardiac death, myocardial infarction, or target vessel revascularization) at 9 months. An additional secondary end point was evaluation of major adverse cardiac events (cardiac death, myocardial infarction, or target lesion revascularization) at 9 and 12 months.

Results Angiographic in-segment late loss was significantly less in the everolimus-eluting stent group compared with the paclitaxel group (mean, 0.14 [SD, 0.41] mm vs 0.28 [SD, 0.48] mm; difference, –0.14 [95% CI, –0.23 to –0.05]; $P \leq .004$). The everolimus stent was noninferior to the paclitaxel stent for target vessel failure at 9 months (7.2% vs 9.0%, respectively; difference, –1.9% [95% CI, –5.6% to 1.8%]; relative risk, 0.79 [95% CI, 0.51 to 1.23]; $P < .001$). The everolimus stent compared with the paclitaxel stent resulted in significant reductions in composite major adverse cardiac events both at 9 months (4.6% vs 8.1%; relative risk, 0.56 [95% CI, 0.34 to 0.94]; $P = .03$) and at 1 year (6.0% vs 10.3%; relative risk, 0.58 [95% CI, 0.37 to 0.90]; $P = .02$), due to fewer myocardial infarctions and target lesion revascularization procedures.

Conclusions In this large-scale, prospective randomized trial, an everolimus-eluting stent compared with a paclitaxel-eluting stent resulted in reduced angiographic late loss, noninferior rates of target vessel failure, and fewer major adverse cardiac events during 1 year of follow-up.

Trial Registration clinicaltrials.gov Identifier: NCT00180479

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BY ENLARGING THE ARTERIAL lumen and sealing dissection planes, stent implantation relieves coronary flow obstruction at the site of atherosclerotic disease. However, injury to the tunica media results in excessive neointimal hyperplasia in approximately 20% to 30% of patients treated with bare-metal stents, which results in recurrent ischemia often necessitating rehospitalization for repeat percutaneous coronary intervention or coronary artery bypass graft surgery.[1] Drug-eluting stents combine the mechanical scaffolding properties of metallic stents with the site-specific delivery of an antiproliferative agent designed to inhibit vascular responses to arterial injury, thereby reducing restenosis. The polymer-regulated, site-specific delivery of paclitaxel and sirolimus have been shown to inhibit tissue growth after coronary stent implantation and to improve long-term event-free survival compared with bare-metal stents.[2,3] However, restenosis still occurs, and the incidence of stent thrombosis, especially after

For editorial comment see p 1952.

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the first year of implantation, is increased with these drug-eluting stents compared with their bare-metal counterparts,[4,5] likely due to delayed and incomplete endothelialization.[6,7]

Newer drug-eluting stents are being designed with the goal of enhanced safety, efficacy, or both compared with previous devices. Everolimus, a semisynthetic macrolide immunosuppressant, is an analogue of rapamycin, which binds to cytosolic FKBP12 and subsequently to the mammalian target of rapamycin, thereby blocking the stimulatory effects of growth factors and cytokines, which are released after vascular injury. As a result, cell cycle progression is blocked between the G1 and S phases, inhibiting smooth muscle cell proliferation.[8]

Everolimus has been shown to prevent cardiac allograft vasculopathy,[9] which histologically resembles the neointimal hyperplasia that develops after coronary stent implantation.[10] An everolimus-eluting stent has been designed in which the drug is released from a thin (7.8-μm), nonadhesive, durable, biocompatible fluoropolymer coated onto a low-profile (0.0032-in [0.0813-mm] strut thickness), flexible cobalt-chromium stent. Preclinical studies have shown more rapid endothelialization with this stent compared with sirolimus-eluting and paclitaxel-eluting stents.[11] Following favorable results with this device in 1 small and 1 moderate-sized randomized study in Europe,[12,13] the large-scale SPIRIT III trial was performed to evaluate the everolimus-eluting stent in comparison to a widely used paclitaxel-eluting stent in patients with coronary artery disease.

METHODS

Study Population, Device Description, and Protocol

SPIRIT III was a prospective, multicenter, randomized, single-blind, controlled clinical trial in which 1002 patients with either 1 or 2 de novo native coronary artery lesions (maximum 1 lesion per epicardial coronary artery) were randomized in a 2:1 ratio to receive the polymer-based everolimus-eluting stent (XIENCE V; Abbott Vascular, Santa Clara, California) or the polymer-based paclitaxel-eluting stent (TAXUS EXPRESS2; Boston Scientific, Natick, Massachusetts). Patients aged 18 years or older with stable or unstable angina or inducible ischemia undergoing percutaneous coronary intervention were considered for enrollment.

Clinical exclusion criteria included percutaneous intervention in the target vessel either prior to or planned within 9 months after the index procedure; intervention in a nontarget vessel within 90 days prior to or planned within 9 months after the index procedure; prior coronary brachytherapy at any time; acute or recent myocardial infarction with elevated cardiac biomarker levels; left ventricular ejection fraction less than 30%; prior or planned organ transplantation; current or planned chemotherapy for malignancy; known immunologic or autoimmune disease or prescribed immunosuppressive medication; use of chronic anticoagulation; contraindications or allergy to aspirin, heparin, and bivalirudin, thienopyridines, everolimus, cobalt, chromium, nickel, tungsten, acrylic, or fluoropolymers, or to iodinated contrast that cannot be premedicated; elective surgery planned within 9 months after the procedure, necessitating antiplatelet agent discontinuation; platelet count less than 100 000 cells/μL or greater than 700 000 cells/μL, white blood cell count less than 3000 cells/μL, serum creatinine level greater than 2.5 mg/dL (to convert to μmol/L, multiply by 88.4), or dialysis or liver disease; recent major bleeding, hemorrhagic diathesis, or objection to blood transfusions; stroke or transient ischemic attack within 6 months; comorbid conditions that limit life expectancy to less than 1 year or that could affect protocol compliance; positive pregnancy test result, lactation, or planned pregnancy within 1 year after enrollment; and participation in another investigational study that has not yet reached its primary end point. The study was approved by the institutional review board at each participating center, and consecutive, eligible patients signed written informed consent.

Prior to catheterization, an electrocardiogram was performed, creatine phosphokinase and isoenzyme levels were measured, and 300 mg or more of aspirin was administered. A 300-mg or greater oral dose of clopidogrel was recommended preprocedure and required in all cases within 1 hour after stent implantation. Procedural anticoagulation was achieved with either unfractionated heparin or bivalirudin per standard of care, and use of glycoprotein IIb/IIIa inhibitors was per operator discretion. Angiographic eligibility was assessed following mandatory predilatation. The reference vessel diameter of all study lesions was required to be between 2.5 mm and 3.75 mm, and the lesion length was required to be 28 mm or less, both by visual assessment, representing the on-label lesion dimensions for which the paclitaxel-eluting stent has been approved by the US Food and Drug Administration (FDA) for use in the United States. Other angiographic exclusion criteria included ostial or left main lesions; bifurcation lesions with either side branch more than 50% stenosed or more than 2 mm in diameter or requiring predilatation; excessive proximal tortuosity, lesion angulation or calcification, or thrombus; lesion located within a bypass graft conduit; diameter stenosis less than 50% or 100%; or the presence of lesions with greater than 40% stenosis within the target vessel or likelihood that additional percutaneous intervention would be required within 9 months.

Following confirmation of angiographic eligibility, telephone randomization was performed in randomly alternating blocks of 3 and 6 patients using an automated voice response system, stratified by the presence of diabetes, planned dual-vessel treatment, and study site. For this trial everolimus-eluting stents were available in 2.5-, 3.0-, and 3.5-mm diameters, and in 8-, 18-, and 28-mm lengths. The full range of US-manufactured paclitaxel-eluting stents were available, ranging from 2.5 to 3.5 mm in diameter and from 8 to 32 mm in length. An appropriate-length stent was selected sufficient to cover approximately 3 mm of nondiseased tissue on either side of the lesion. In patients receiving multiple

stents for a single lesion, 1 to 4 mm of stent overlap was recommended. Additional study stents were permitted for edge dissections greater than type C or otherwise suboptimal results, and postdilation was at operator discretion.

Following the procedure, an electrocardiogram was performed and cardiac enzyme levels were measured. The protocol recommended that patients receive aspirin (≥80 mg/d) indefinitely and clopidogrel (75 mg/d) for a minimum of 6 months. Clinical follow-up was scheduled at 30 (±7) days, 180 (±14) days, 240 (±28) days, 270 (±14) days, 365 (±28) days, and then yearly (±28 days) through 5 years. Although the operators were by necessity unblinded during the stent implantation procedure, the patient and staff involved in follow-up assessments remained blinded through the follow-up period, with a standardized follow-up interview script used to reduce bias. Protocol-specified angiographic follow-up was scheduled at 240 (±28) days in the first 564 patients enrolled. Among these patients, intravascular ultrasound immediately following stent implantation and at follow-up was intended in 240 patients at selected sites.

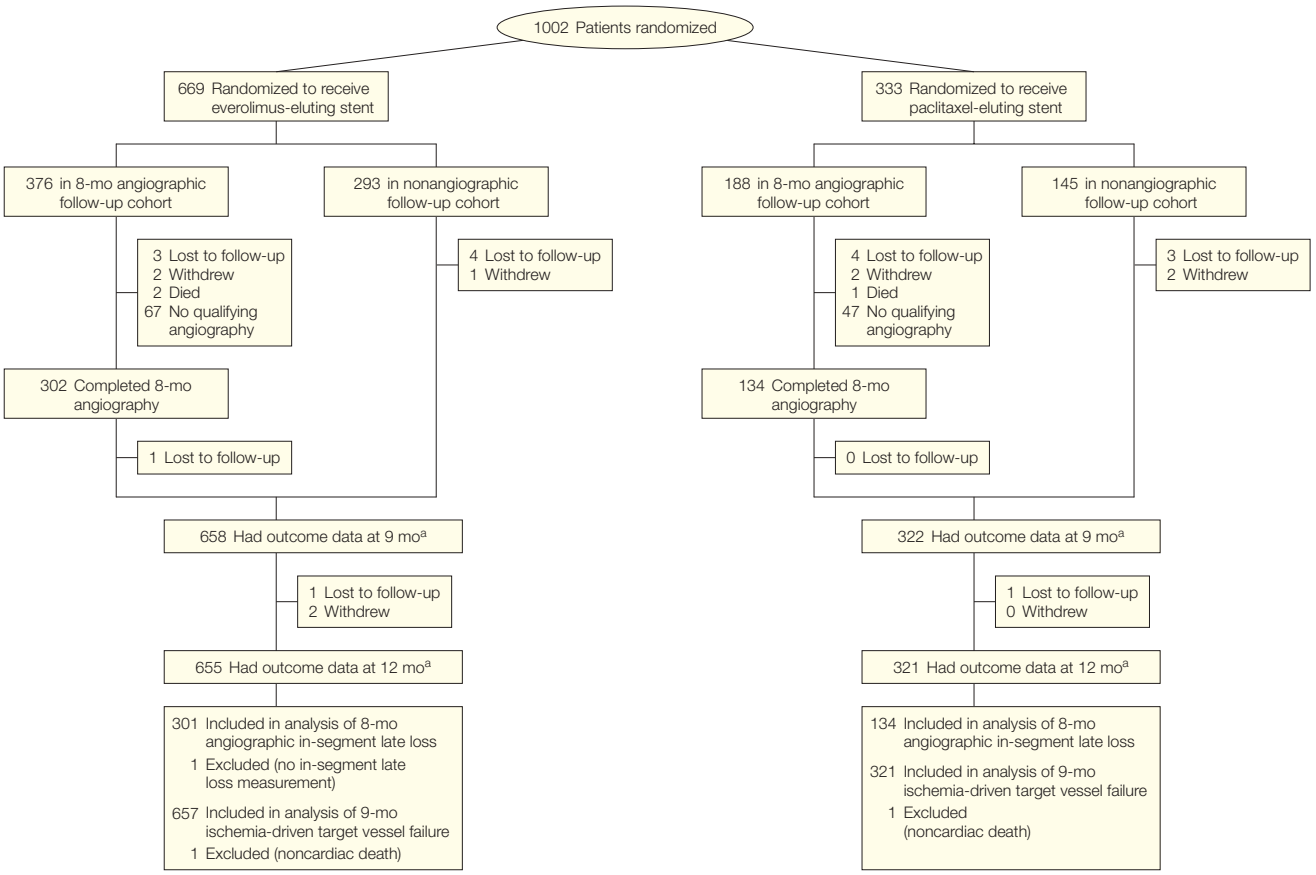
Data Management

Independent study monitors verified 100% of case report form data on-site. Data were stored in a database maintained by Abbott Vascular. All major adverse cardiac events were adjudicated by an independent committee blinded to treatment allocation after review of original source documentation. A second clinical events committee blinded to randomization performed a post hoc adjudication of stent thrombosis using the Academic Research Consortium definitions.[14] A data and safety monitoring board periodically reviewed blinded safety data, each time recommending that the study continue without modification. Independent core angiographic and intravascular ultrasound analyses were performed by technicians blinded to treatment assignment and clinical outcomes using validated methods as previously described.[15,16]

End Points and Definitions

The primary end point was in-segment late loss at 240 days (defined as the difference in the minimal luminal diameter assessed immediately after the pro-

Figure 1. Patient Flow and Follow-up in the SPIRIT III Trial



Prior to the 1-year follow-up period, 14 of 669 patients (2.1%) randomized to receive the everolimus-eluting stent either withdrew (n=5) or were lost to follow-up (n=9), and 12 of 333 patients (3.6%) randomized to receive the paclitaxel-eluting stent either withdrew (n=4) or were lost to follow-up (n=8).
[a]Nine-month follow-up was performed at 270 (±14) days; 12-month follow-up, at 365 (±28) days.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Everolimus-Eluting Stent	Paclitaxel-Eluting Stent
Demographics, No./total (%)	669	332
Age, mean (SD), y	63.2 (10.5)	62.8 (10.2)
Men	469/669 (70.1)	218/332 (65.7)
Hypertension	510/669 (76.2)	245/331 (74.0)
Hypercholesterolemia	489/659 (74.2)	233/326 (71.5)
Diabetes mellitus		
Any	198/669 (29.6)	92/330 (27.9)
Requiring insulin	52/669 (7.8)	18/330 (5.5)
Current smoker	154/659 (23.4)	73/324 (22.5)
Prior myocardial infarction	130/652 (19.9)	59/327 (18.0)
Unstable angina	123/657 (18.7)	82/327 (25.1)
Target vessel, No./total (%)	772	383
Left anterior descending	317/768 (41.3)	164/382 (42.9)
Left circumflex	212/768 (27.6)	108/382 (28.3)
Right coronary	238/768 (31.0)	109/382 (28.5)
Left main, protected	1/768 (0.1)	1/382 (0.3)
Target lesion, mean (SD)	772	383
Reference vessel diameter, mm	2.77 (0.45)	2.76 (0.46)
Minimal luminal diameter, mm	0.82 (0.41)	0.83 (0.40)
Diameter stenosis, %	70.0 (13.3)	69.4 (13.6)
Lesion length, mm	14.7 (5.6)	14.7 (5.7)

cedure and at angiographic follow-up, measured within the margins, 5 mm proximal and 5 mm distal to the stent). To avoid interlesion clustering of restenosis in patients receiving stents for multiple lesions[17] (which would have required correction with multilevel generalized estimating equations), the protocol specified that for patients in whom 2 lesions were treated a single lesion (the analysis lesion) would be randomly selected by computer for analysis of late loss. All randomized lesions were included in the analyses for all other angiographic end points.

The major secondary end point was ischemia-driven target vessel failure at 270 days, defined as the composite of cardiac death (death in which a cardiac cause could not be excluded), myocardial infarction (Q-wave or non–Q-wave), and ischemia-driven target vessel revascularization by either percutaneous coronary intervention or bypass graft surgery. Target vessel (or lesion) revascularization was considered to be ischemia-driven if associated with a positive functional study result, a target vessel (or lesion) diameter stenosis of 50% or greater by core laboratory quantitative analysis with ischemic symptoms, or a target vessel (or lesion) diameter stenosis of 70% or greater with or without documented ischemia.

An additional prespecified secondary end point included major adverse cardiac events at 9 months and 1 year, defined as the composite of cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization. Myocardial infarction was defined either as the development of new pathologic Q waves 0.4 seconds or longer in duration in 2 or more contiguous leads or as an elevation of creatine phosphokinase levels to more than 2 times normal with positive levels of creatine phosphokinase MB. Stent thrombosis was prospectively defined by protocol as an acute coronary syndrome with angiographic evidence of thrombus within or adjacent to a previously treated target lesion or, in the absence of angiography, as any unexplained death or acute myocardial infarction with ST-segment elevation or new Q waves in the distribution of the target lesion occurring within 30 days. Binary restenosis was defined as 50% or greater diameter stenosis of the treated lesion at angiographic follow-up. Other angiographic and intravascular ultrasound parameters were defined as previously described.[15,16]

Statistical Methods

The trial was powered for noninferiority for both the primary end point of in-segment late loss at 8 months among patients in the angiographic follow-up cohort, as well as the major secondary end point of ischemia-driven target vessel failure at 9 months in all enrolled patients. As agreed on with FDA, noninferiority for in-segment late loss would be declared if the upper limit of the 1-sided 97.5% confidence interval (CI) of the difference did not exceed a delta of 0.195 mm from the observed in-segment late lumen loss in the paclitaxel-eluting stent group, equivalent to a 1-sided test with $\alpha = .025$. Assuming a mean late loss of 0.24 (SD, 0.47) mm for both stents, with angiographic follow-up performed in 338 everolimus-eluting stent and 169 paclitaxel-eluting stent analysis lesions, the trial had 99% power to demonstrate noninferiority for in-segment late loss. Sequential superiority testing was prespecified if noninferiority for late loss was met. Noninferiority for ischemia-driven target vessel failure was declared if the upper limit of the 1-sided 95% CI of the difference did not exceed a delta of 5.5% from the observed paclitaxel-eluting stent control event rate. Assuming a target vessel failure rate of 9.4% for both stents, with 9-month clinical follow-up performed in 660 patients randomized to receive the everolimus-eluting stent and 330 to receive the paclitaxel-eluting stent, the trial had 89% power to demonstrate noninferiority for target vessel failure. Noninferiority for the prespecified powered primary as well as the major secondary end points had to be met for the trial to be considered successful, and as such both are considered coprimary end points.

Categorical variables were compared by Fisher exact test. Continuous variables are presented as mean (SD) and were compared by *t* test. The statistical analysis plan prespecified that all primary and secondary analyses

would be performed in the intent-to-treat population, consisting of all patients randomized in the study, regardless of the treatment actually received. However, patients lost to follow-up in whom no event had occurred prior to the follow-up windows were not included in the denominator for calculations of binary end points. Survival curves using all available follow-up data were also constructed for time-to-event variables using Kaplan-Meier estimates and compared by log-rank test. Superiority testing was performed after demonstration of noninferiority for the primary and major secondary end points[18] and for all other secondary end points using a 2-sided $\alpha = .05$. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patients and Enrollment

Between June 22, 2005, and March 15, 2006, 1002 patients were enrolled at 65 US sites and randomized to receive the everolimus-eluting stent (n=669) or the paclitaxel-eluting stent (n=333) (FIGURE 1). One patient in the paclitaxel group did not sign informed consent; thus, his or her data are unavailable. Baseline characteristics of the patients were well matched between the 2 groups (TABLE 1), except for slightly more unstable angina in the paclitaxel group ($P = .02$). The mean number of lesions stented was 1.2 (SD, 0.4) in each group; 2 lesions were treated in 15.4% of patients in each group, whereas the remainder had 1 lesion treated. Lesion characteristics as measured by quantitative coronary angiography were also similar between the 2 groups (Table 1).

Procedural Results and Angiographic Outcomes

As shown in TABLE 2, the total stent length per lesion was slightly greater in the everolimus group, likely due to the fewer stent lengths available for accurate lesion matching. Conversely, implantation pressure was slightly less in the group receiving everolimus stents. Other procedural variables were well matched between the groups. Acute postprocedure angiographic measures were also not significantly different between the 2 groups.

Angiographic follow-up at 8 months was completed in 77% of eligible patients (Figure 1). The primary end point of in-segment late loss in the analysis lesion was significantly less in the everolimus group compared with the paclitaxel group (0.14 [SD, 0.41] mm [n=301 lesions] vs 0.28 [SD, 0.48] mm [n=134 lesions]; difference, –0.14 [95% CI, –0.23 to –0.05]; $P_{\text{noninferiority}} < .001$; $P_{\text{superiority}} = .004$). In-stent late loss in the analysis lesion was also significantly less in the everolimus group (0.16 [SD, 0.41] mm vs 0.31 [SD, 0.55] mm; difference, –0.15 [95% CI, –0.25 to –0.04]; $P_{\text{noninferiority}} < .001$; $P_{\text{superiority}} = .006$). Similar results were found when all lesions were considered (Table 2). As a result, strong trends were present toward a reduction in binary in-stent and in-segment restenosis with the everolimus stent compared with the paclitaxel stent (Table 2). No aneurysms were present at 8 months in either group.

Intravascular Ultrasound Findings

Volumetric intravascular ultrasound data were available at 8 months in 101

Table 2. Procedural Results and Angiographic Outcomes

Result/Outcome	Everolimus-Eluting Stent	Paclitaxel-Eluting Stent	*P* Value
Procedural variables, mean (SD)			
No. of patients	669	332	
No. of stents per patient	1.3 (0.6)	1.3 (0.5)	.27
No. of stents per lesion	1.2 (0.4)	1.1 (0.3)	.07
Maximum stent diameter per lesion, mm	3.0 (0.4)	3.0 (0.4)	>.99
Maximum stent to reference vessel diameter ratio	1.1 (0.1)	1.1 (0.1)	.56
Total stent length per lesion, mm	22.8 (8.4)	21.6 (7.8)	.02
Total stent to lesion length ratio	1.6 (0.5)	1.5 (0.5)	.01
Maximum pressure, atm	14.8 (2.9)	15.1 (2.6)	.049
Glycoprotein IIb/IIIa inhibitors used, No./total (%)	184/669 (27.5)	82/332 (24.7)	.36
Postprocedural angiographic results, mean (SD)			
No. of lesions	772	383	
Minimal luminal diameter, mm			
In-stent	2.71 (0.43)	2.74 (0.41)	.38
In-segment	2.37 (0.45)	2.36 (0.45)	.73
Diameter stenosis, %			
In-stent	0.3 (8.9)	–0.2 (9.9)	.37
In-segment	13.5 (7.6)	14.4 (7.1)	.06
Acute gain, mm			
In-stent	1.89 (0.48)	1.91 (0.47)	.56
In-segment	1.54 (0.51)	1.53 (0.50)	.62
8-mo angiographic follow-up, mean (SD)[a]			
No. of lesions	344	158	
Reference vessel diameter, mm	2.77 (0.43)	2.78 (0.42)	.84
Minimal luminal diameter, mm			
In-stent	2.56 (0.53)	2.45 (0.65)	.07
In-segment	2.22 (0.53)	2.12 (0.60)	.08
Diameter stenosis, %			
In-stent	5.9 (16.4)	10.3 (21.4)	.02
In-segment	18.8 (14.4)	22.8 (16.4)	.008
Late loss, mm			
In-stent	0.16 (0.41)	0.30 (0.53)	.002
In-segment	0.14 (0.39)	0.26 (0.46)	.003
Binary restenosis, No./total (%)			
In-stent	8/343 (2.3)	9/158 (5.7)	.06
In-segment	16/344 (4.7)	14/158 (8.9)	.07

[a] Analysis of all lesions.

lesions in the everolimus group and 41 in the paclitaxel group. The everolimus stent compared with the paclitaxel stent resulted in significantly less neointimal hyperplasia (10.13 [SD, 11.46] mm^3 vs 20.87 [SD, 31.51] mm^3, $P=.04$) and percent volume obstruction (6.9% [SD, 6.4%] vs 11.2% [SD, 9.9%], $P=.01$). Paired immediate postprocedure and follow-up intravascular ultrasound studies were available in 90 lesions in the everolimus group and 43 in the paclitaxel group. Comparing the everolimus and paclitaxel stents, there were no significant differences detected in the rates of incomplete stent apposition either at the completion of the procedure (34.4% vs 25.6%, respectively; $P=.33$) or at 8 months (25.6% vs 16.3%, $P=.27$). Late acquired incomplete stent apposition was infrequent in both groups (1.1% vs 2.3%, $P=.54$).

Clinical Outcomes

At 30 days there tended to be fewer myocardial infarctions among the patients randomized to receive the everolimus stent compared with the paclitaxel stent (7/667 patients [1.0%] vs 9/330 [2.7%], respectively; relative risk, 0.38 [95% CI, 0.14 to 1.02]; $P=.06$), with comparable rates of cardiac death (0% in both groups) and target lesion revascularization (3/667 patients [0.4%] vs 1/330 [0.3%], respectively; relative risk, 1.48 [95% CI, 0.15 to 14.21]; $P>.99$). At 9 months, everolimus stents compared with paclitaxel stents were noninferior for the major secondary end point of ischemia-driven target vessel failure (47/657 patients [7.2%] vs 29/321 [9.0%], respectively; difference, –1.9% [95% CI, –5.6% to 1.8%]; relative risk, 0.79 [95% CI, 0.51 to 1.23]; $P_{noninferiority}<.001$; $P_{superiority}=.31$). A nonsignificant trend was also present at 1 year for a 24% reduction in target vessel failure in patients randomized to receive everolimus stents rather than paclitaxel stents (56/653 patients [8.6%] vs 36/320 [11.3%], respectively; relative risk, 0.76 [95% CI, 0.51 to 1.13]; $P=.20$). Use of the everolimus stent compared with the paclitaxel stent resulted in significant reductions in the secondary end point of composite major adverse cardiac events, both at 9 months (30/657 patients [4.6%] vs 26/321 [8.1%]; relative risk, 0.56 [95% CI, 0.34 to 0.94]; $P=.03$) and at 1 year (39/653 patients [6.0%] vs 33/320 [10.3%]; relative risk, 0.58 [95% CI, 0.37 to 0.90]; $P=.02$).

As shown in TABLE 3, there were no significant differences between the everolimus stent and the paclitaxel stent in the 1-year rates of death (all cause, cardiac, or noncardiac) or of myocardial infarction (all, Q-wave, or non–Q-wave). Similarly, there were no significant differences between the 2 devices in the rates of stent thrombosis, either early (≤30 days) or late (>30 days), whether analyzed by the prespecified protocol definition or by post hoc Academic Research Consortium definitions. There were also no statistically significant differences in the rates of target lesion revascularization, target vessel revascularization, or target vessel failure between the 2 stents at 1 year. As shown in FIGURE 2, the difference between the hazard curves for major adverse cardiac events became apparent in the early postprocedural period due to fewer myocardial infarctions with the everolimus stent, and then spread further between 6 and 12 months due to fewer target lesion revascularization procedures with the everolimus stent. Of the 15 and 12 patients in the everolimus and paclitaxel groups who had a protocol-defined ischemic target lesion revascularization event by 1 year, 5 and 4 patients, respectively (33.3% in each group) underwent revascularization solely on the basis of a diameter stenosis greater than 70% demonstrated by quantitative coronary angiography. At 365 days, aspirin was being taken by 94.9% and 92.4%

Table 3. Clinical Outcomes at 1 Year

Outcome	No./Total (%)		*P* Value
	Everolimus-Eluting Stent (n = 655)	Paclitaxel-Eluting Stent (n = 321)	
Death	8/655 (1.2)	4/321 (1.2)	>.99
Cardiac	5/655 (0.8)	3/321 (0.9)	.72
Noncardiac	3/655 (0.5)	1/321 (0.3)	>.99
Myocardial infarction[a]	18/653 (2.8)	13/320 (4.1)	.33
Q-wave	2/653 (0.3)	1/320 (0.3)	>.99
Non–Q-wave	16/653 (2.5)	12/320 (3.8)	.31
Death or myocardial infarction	24/654 (3.7)	16/321 (5.0)	.39
Cardiac death or myocardial infarction[a]	22/653 (3.4)	15/320 (4.7)	.37
Stent thrombosis			
Protocol definition	5/647 (0.8)	2/317 (0.6)	>.99
≤30 d	3/667 (0.4)	0/330 (0)	.55
>30 d	2/646 (0.3)	2/317 (0.6)	.60
ARC			
Definite	5/652 (0.8)	0/319 (0)	.18
Probable	2/652 (0.3)	2/319 (0.6)	.60
Possible	4/652 (0.6)	2/319 (0.6)	>.99
Definite or probable	7/652 (1.1)	2/319 (0.6)	.73
Any	11/652 (1.7)	4/319 (1.3)	.78
Target lesion revascularization	22/655 (3.4)	18/321 (5.6)	.12
Target vessel revascularization	40/655 (6.1)	24/321 (7.5)	.41
Target vessel revascularization remote	20/655 (3.1)	14/321 (4.4)	.35
Major adverse cardiac events[a]	39/653 (6.0)	33/320 (10.3)	.02
Target vessel failure[a]	56/653 (8.6)	36/320 (11.3)	.20

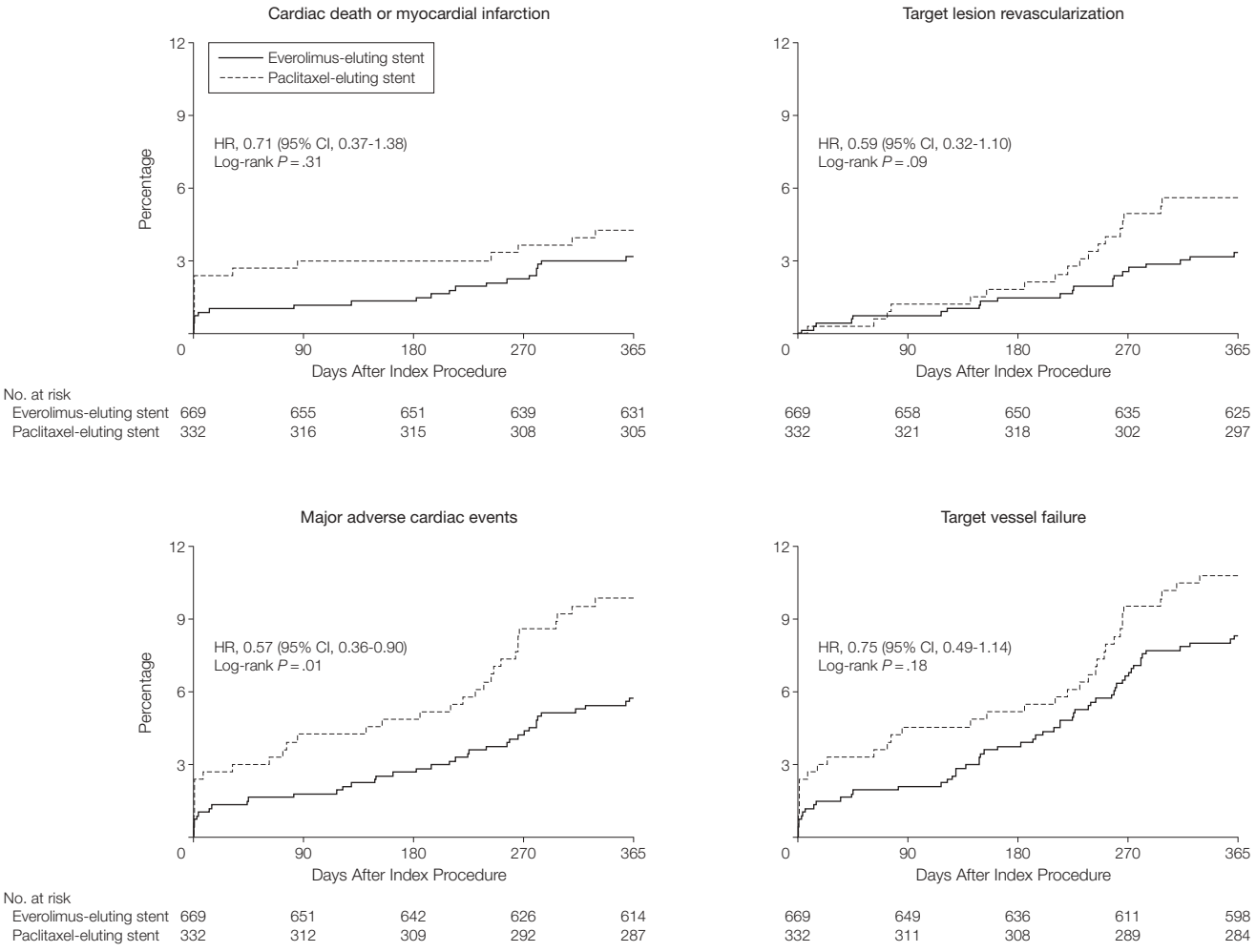
Abbreviations: ARC, Academic Research Consortium.[14]
[a] Per the statistical analysis plan, since the composite target vessel failure and major adverse cardiac event end points included cardiac deaths only, patients with noncardiac deaths were excluded from the denominator.

of patients receiving everolimus stents and paclitaxel stents, respectively (P=.15), and a thienopyridine (clopidogrel or ticlopidine) was being taken by 71.2% and 70.4%, respectively (P=.82).

Subgroup Analysis

A post hoc linear regression analysis with formal interaction testing was performed to explore whether the reduction of the primary end point of in-segment late loss at 8 months with the everolimus stent compared with the paclitaxel stent was consistent across important subgroups (of which diabetes and the number of treated vessels were prespecified). As shown in FIGURE 3, there were no significant interactions between treatment assignment and angiographic outcomes among 7 subgroups, with the exception of age. Logistic regression analysis with interaction testing was also performed to explore whether the reduction in major adverse cardiac events with the everolimus stent compared with the paclitaxel stent present at 1 year was consistent across important subgroups. As shown in FIGURE 4, there were no significant interactions between treatment assignment and outcomes at 1 year among 8 subgroups, with the exception of patients with diabetes. The relative reduction in major adverse cardiac events with everolimus stents compared with paclitaxel stents was comparable in patients both undergoing and not undergoing 8-month follow-up angiography. Among patients in the angiographic follow-up cohort, target lesion revascularization in the everolimus and paclitaxel stent groups was required in 15 of 368 (4.1%) vs 12 of 181 (6.6%) patients, respectively (relative

Figure 2. Time-to-Event Curves for Cardiac Death or Myocardial Infarction, Target Lesion Revascularization, Major Adverse Cardiac Events, and Target Vessel Failure Among Patients Randomized to Receive the Everolimus-Eluting Stent and the Paclitaxel-Eluting Stent



Event rates presented here were calculated by Kaplan-Meier methods and compared with the log-rank test and differ slightly from those in the text and Table 3, which were calculated as categorical variables and compared with the Fisher exact test. In each panel, initial number at risk for the paclitaxel stent differs from the number randomized because 1 patient did not sign informed consent. CI indicates confidence interval; HR, hazard ratio.

risk, 0.61 [95% CI, 0.29 to 1.29]; *P*=.21), whereas in the nonangiographic follow-up cohort the target lesion revascularization rates were 7 of 285 (2.5%) vs 6 of 139 (4.3%), respectively (relative risk, 0.57 [95% CI, 0.19 to 1.66]; *P*=.37).

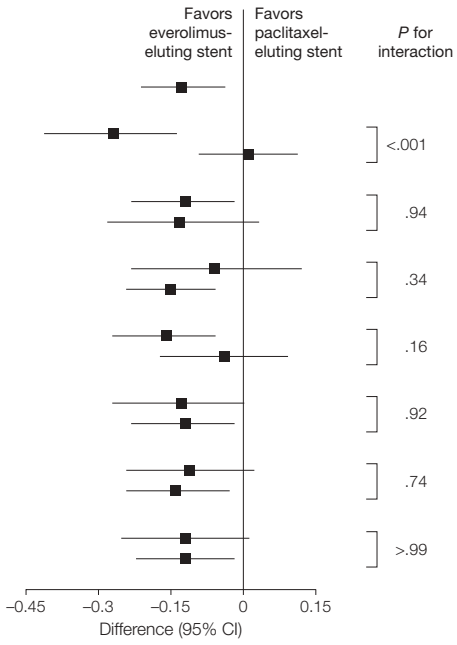
COMMENT

This large-scale, prospective, randomized, single-blind, controlled study demonstrates that an everolimus-eluting stent compared with a widely used paclitaxel-eluting stent results in a significant reduction in angiographic in-segment late loss at 8 months, with noninferior 9-month rates of ischemia-driven target vessel failure. Thus, the 2 prespecified FDA regulatory requirements required for the trial to be considered successful were met. The reduction in late loss was confirmed by the findings from intravascular ultrasound, which demonstrated an approximate 50% reduction in volumetric neointimal hyperplasia. As a result, even though the trial was not powered for a reduction in binary angiographic restenosis, a strong trend was present in this direction favoring the everolimus-eluting stent.

Notably, the everolimus stent compared with the paclitaxel stent resulted in a significant 42% reduction in major adverse cardiac events at 1 year. As such, the present study is the first pivotal randomized trial to demonstrate enhanced event-free survival with a new stent compared with any of the 3 drug-eluting stents commercially available in the United States for on-label lesions (ie, those for which treatment with drug-eluting stents has been approved by the FDA). As defined in this trial, major adverse cardiac events is a composite measure of safety (cardiac death and myocardial infarction) and stent efficacy (target lesion revascularization), which is more specific to the action of the stent than is target vessel failure (which includes the occurrence of target vessel revascularization remote from the target lesion, which would not be expected to be affected by stent implantation). The reduction in composite major adverse cardiac events with the everolimus stent was attributable to fewer postprocedural non–Q-wave myocardial infarctions and late target lesion revascularizations due to the reduction in restenosis. In this regard the results of SPIRIT III confirm and extend those from the smaller (300 patients) randomized SPIRIT II trial, in which the 1-year rates of major adverse cardiac events (using the same definition) were decreased from 9.2% with a paclitaxel-eluting stent to 2.7% with an everolimus-eluting stent (*P*=.04), also due to fewer cardiac deaths, myocardial infarctions, and target lesion revascularizations.[19] Reduction in procedural-related myonecrosis with the everolimus stent may result from less side-branch compromise due to the thinner polymer (7.8 µm vs 16.0 µm) and total polymer plus stent strut width (89 vs 148 µm) compared with the paclitaxel stent,[20] though detailed angio-

Figure 3. Subgroup Analyses of the Primary End Point of 8-Month Angiographic In-Segment Late Loss Among Patients Randomized to Receive the Everolimus-Eluting Stent vs the Paclitaxel-Eluting Stent

	No. of randomized lesions		In-segment luminal late loss, mean (SD), mm			
	Everolimus-eluting stent	Paclitaxel-eluting stent	Everolimus-eluting stent	Paclitaxel-eluting stent	Difference (95% CI)	*P* for interaction
Angiographic follow-up cohort	343	158	0.14 (0.39)	0.26 (0.46)	–0.13 (–0.21 to 0.04)	
Age						
≥Median (63 y)	171	76	0.12 (0.37)	0.39 (0.55)	–0.27 (–0.41 to 0.14)	<.001
<Median	172	82	0.16 (0.42)	0.15 (0.33)	0.01 (–0.09 to 0.11)	
Sex						
Men	250	108	0.13 (0.34)	0.25 (0.49)	–0.12 (–0.23 to –0.02)	.94
Women	93	50	0.16 (0.51)	0.29 (0.41)	–0.13 (–0.28 to 0.03)	
Diabetes						
Yes	96	31	0.18 (0.51)	0.24 (0.40)	–0.06 (–0.23 to 0.12)	.34
No	247	127	0.12 (0.34)	0.27 (0.48)	–0.15 (–0.24 to –0.06)	
No. of treated vessels						
Single	258	110	0.13 (0.41)	0.30 (0.49)	–0.16 (–0.27 to –0.06)	.16
Dual	85	48	0.14 (0.33)	0.18 (0.39)	–0.04 (–0.17 to 0.09)	
Target vessel						
LAD	135	68	0.13 (0.40)	0.26 (0.49)	–0.13 (–0.27 to 0.00)	.92
Non-LAD	208	90	0.14 (0.39)	0.26 (0.45)	–0.12 (–0.23 to –0.02)	
RVD						
>Median (2.775 mm)	166	88	0.18 (0.38)	0.29 (0.54)	–0.11 (–0.24 to 0.02)	.74
≤Median	177	70	0.10 (0.41)	0.24 (0.36)	–0.14 (–0.24 to –0.03)	
Lesion length						
>Median (13.7 mm)	169	82	0.19 (0.47)	0.31 (0.51)	–0.12 (–0.25 to 0.01)	>.99
≤Median	174	74	0.09 (0.30)	0.21 (0.40)	–0.12 (–0.22 to –0.02)	

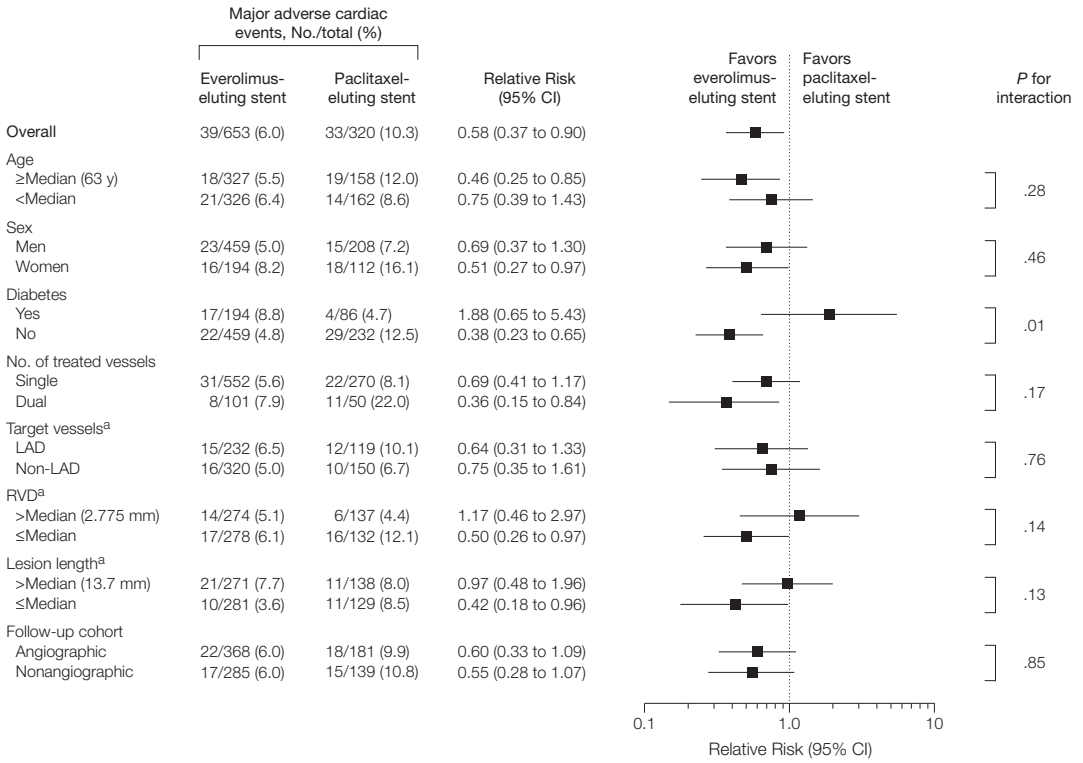


Probability for interaction represents the likelihood for interaction between the variable and the relative treatment effect. CI indicates confidence interval; LAD, left anterior descending; RVD, reference vessel diameter.

graphic study is required to confirm this possibility. Importantly, there were no significant differences in the occurrence of stent thrombosis through 1 year between these 2 devices, though this trial was underpowered to reliably evaluate this event; also, longer-term follow-up is required, because the incremental risk of stent thrombosis with drug-eluting stents may emerge beyond 1 year.[4] The lower rate of target lesion revascularization with the everolimus stent compared with the paclitaxel stent may be directly attributed to the reduction in late loss and smaller follow-up diameter stenosis in the target lesion, as recently described.[21]

The reduction in in-segment late loss with the everolimus stent compared with the paclitaxel stent was consistent across multiple important subgroups except when stratified by age. No significant differences in angiographic outcomes were present between the 2 stents in young patients, whereas assignment to receive the everolimus stent rather than the paclitaxel stent was associated with a marked reduction in late loss in elderly patients. Given the lack of an interaction with reference vessel diameter and lesion length, an explanation underlying this finding is not immediately evident. Of note, no interaction was present between diabetic status and angiographic late loss, signifying a significant reduction in in-segment late loss with the everolimus stent compared with the paclitaxel stent in patients both with and without diabetes. In contrast, a significant interaction was present between diabetes and stent type on the major adverse cardiac event end point, a finding that contributes to the conflicting reports from prior studies examining the relative safety and efficacy of paclitaxel-eluting compared with sirolimus-eluting stents in patients with diabetes.[22-25] However, this difference was driven by the 62% lower rate of major adverse cardiac events in patients with diabetes who were treated with paclitaxel stents compared with patients without diabetes who also were treated with paclitaxel stents, an unlikely finding that may have been due to chance alone. The differences between the 2 devices were also less apparent in larger vessels (which, compared with small vessels, may be able to accommodate more neointimal hyperplasia before the ischemic threshold is reached)[21] and in longer lesions (which, compared with shorter lesions, may have a greater statistical likelihood of restenosis developing in a

Figure 4. Subgroup Analyses of the 1-Year Rates of Major Adverse Cardiac Events Among Patients Randomized to Receive the Everolimus-Eluting Stent vs the Paclitaxel-Eluting Stent



Probability for interaction represents the likelihood for interaction between the variable and the relative treatment effect. CI indicates confidence interval; LAD, left anterior descending; RVD, reference vessel diameter.
[a]Analysis restricted to patients undergoing treatment of a single lesion.

single spot, despite less volumetric neointimal hyperplasia). Moreover, no differences were evident in the beneficial effect of the everolimus stent compared with the paclitaxel stent in reducing the occurrence of major adverse cardiac events as a function of age. All of these subgroup findings should be considered hypothesis-generating, because subgroup analysis is inherently underpowered and statistical adjustments were not made for multiple comparisons leading to possible false-positive findings.[26]

The strengths and limitations of the present investigation should be considered. That composite major adverse cardiac events have now been shown to be reduced with an everolimus stent compared with a paclitaxel stent in 2 consecutive randomized trials performed at different institutions in different geographies (United States vs Europe and Asia Pacific)[19] increases the likelihood that this finding is real. Despite the dilutive effect of including target vessel revascularization in the target vessel failure end point, a trend was also present toward a 24% reduction with the everolimus stent in this composite measure at 1 year. Moreover, the clinical and angiographic outcomes with the paclitaxel stent in the present study were similar or better than those observed in earlier trials with this device in comparable patients and lesions,[2] and as such underperformance of the control stent does not explain this finding. However, while SPIRIT III is the largest completed trial to date investigating an everolimus-eluting stent, major adverse cardiac events were not the primary end point of this study (nor of SPIRIT II), and therefore this conclusion cannot be considered definitive until prospectively verified in an adequately powered randomized trial. The present trial also was underpowered to examine whether an everolimus stent reduces target lesion revascularization, target vessel revascularization, and target vessel failure as well as the occurrence of low-frequency safety events, compared with a paclitaxel stent. That angiographic follow-up was performed in 43.5% of patients in the present trial further raises concern whether the greater late loss with the paclitaxel stent compared with the everolimus stent may have triggered a greater proportion of excess revascularization procedures in the former group (the "oculostenotic reflex"),[27] although such a bias was not apparent in subgroup analysis. Logistic considerations precluded blinding the operator to the stent type, although clinical follow-up assessment, core laboratory, and clinical events committee personnel were blinded to randomization group, and source-documented ischemia or a severe stenosis by quantitative analysis was required to be present for declaration of target lesion or vessel revascularization. The results of the present trial cannot be extended to patient and lesion types excluded from enrollment. Also, complete screening log data are not available, and thus the proportion of patients undergoing percutaneous coronary intervention who were eligible for enrollment in this study is unknown. Finally, the current study was not designed to elicit other potential advantages of the everolimus stent, such as its greater flexibility and deliverability in complex coronary anatomy.

In summary, in this large-scale, prospective randomized trial, an everolimus-eluting stent compared with a paclitaxel-eluting stent in de novo native coronary artery lesions resulted in reduced angiographic late loss, noninferior rates of target vessel failure, and fewer major adverse cardiac events during 1 year of follow-up.

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Independent Statistical Analysis: The accuracy of the data analysis was independently verified by Martin Fahy, MSc, from the Cardiovascular Research Foundation (CRF), an affiliate of Columbia University College of Physicians and Surgeons. (The dean of Columbia University is responsible for this collaboration with the CRF and empowers an active oversight committee to monitor this relationship and the activities of the CRF.) Mr Fahy received the entire raw database and replicated all of the analyses that were reported in the manuscript, and no discrepancies were discovered. The results reported in this article are the results based on this independent analysis. Neither Mr Fahy nor the CRF received any funding for this independent analysis.

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The XIENCE V™ Everolimus-Eluting Stent

New SPIRIT Clinical Data

Gregg W. Stone, MD

Columbia University Medical Center
The Cardiovascular Research Foundation

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

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Disclosures

- Research support from Abbott Vascular and Boston Scientific

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The XIENCE V SPIRIT Program
(Results reported)

SPIRIT FIRST RCT vs. VISION™	SPIRIT II RCT vs. TAXUS®	SPIRIT III RCT vs. TAXUS®
Safety and performance	Clinical support for CE launch	Pivotal RCT with parallel registries
N = 60	N = 300	N = 1,002 rand
Europe	EU, India, NZ	USA
PI: PW Serruys	PI: PW Serruys	PI: GW Stone
4 year F/U completed	2 year F/U completed	2 year F/U completed

2 year pooled pt level meta-analysis
First time report

SPIRIT II + III Pooled Meta-analysis
Trial Descriptors
(1,302 randomized patients)

	SPIRIT II	SPIRIT III
# Rand. pts, sites	300 pts at 28 sites	1,002 pts at 65 sites
XIENCE V : Taxus	3:1 (223:77)	2:1 (669:333)
Geography	Europe, Asia	USA
RVD (mm)	2.5 – 4.0	2.5 – 3.75
Lesion length (mm)	≤ 28	≤ 28
# lesions, vessels	1-2 lesions, 1/vessel	1-2 lesions, 1/vessel
Clinical FU w/i 1st yr	1, 6, 9, 12 mos	1, 6, 9, 12 mos
Angio FU, completed	275/300 at 6 mos	436/564 at 8 mos

SPIRIT II + III Pooled Meta-analysis
Baseline Features
(1,302 randomized patients)

	XIENCE V (n=892 pts)	TAXUS (n=410 pts)
Age (years)	62.9 ± 10.5	62.6 ± 10.1
Male	70.3%	68.2%
Diabetes	27.9%	27.1%
- treated with insulin	7.1%	5.7%
Hypertension	74.0%	72.3%
Hypercholesterolemia	72.8%	72.1%
Current smoker	25.3%	23.8%
Prior MI	23.7%	19.3%
Unstable angina	20.8%	26.5%

All p = NS

SPIRIT II + III Pooled Meta-analysis

Angiographic Characteristics

(1,501 lesions in 1,302 randomized patients)

		XIENCE V (n=1028 lsns)	TAXUS (n=473 lsns)
Lesion location	LAD	41.1%	43.8%
	LCX	28.0%	26.4%
	RCA	30.7%	29.6%
	LMCA	0.1%	0.2%
QCA	RVD (mm)	2.75 ± 0.47	2.77 ± 0.48
	MLD (mm)	0.88 ± 0.43	0.89 ± 0.41
	% DS	67.7 ±13.6	67.5 ±13.6
	Lsn length (mm)	14.3 ± 5.7	14.5 ± 5.9

All p = NS

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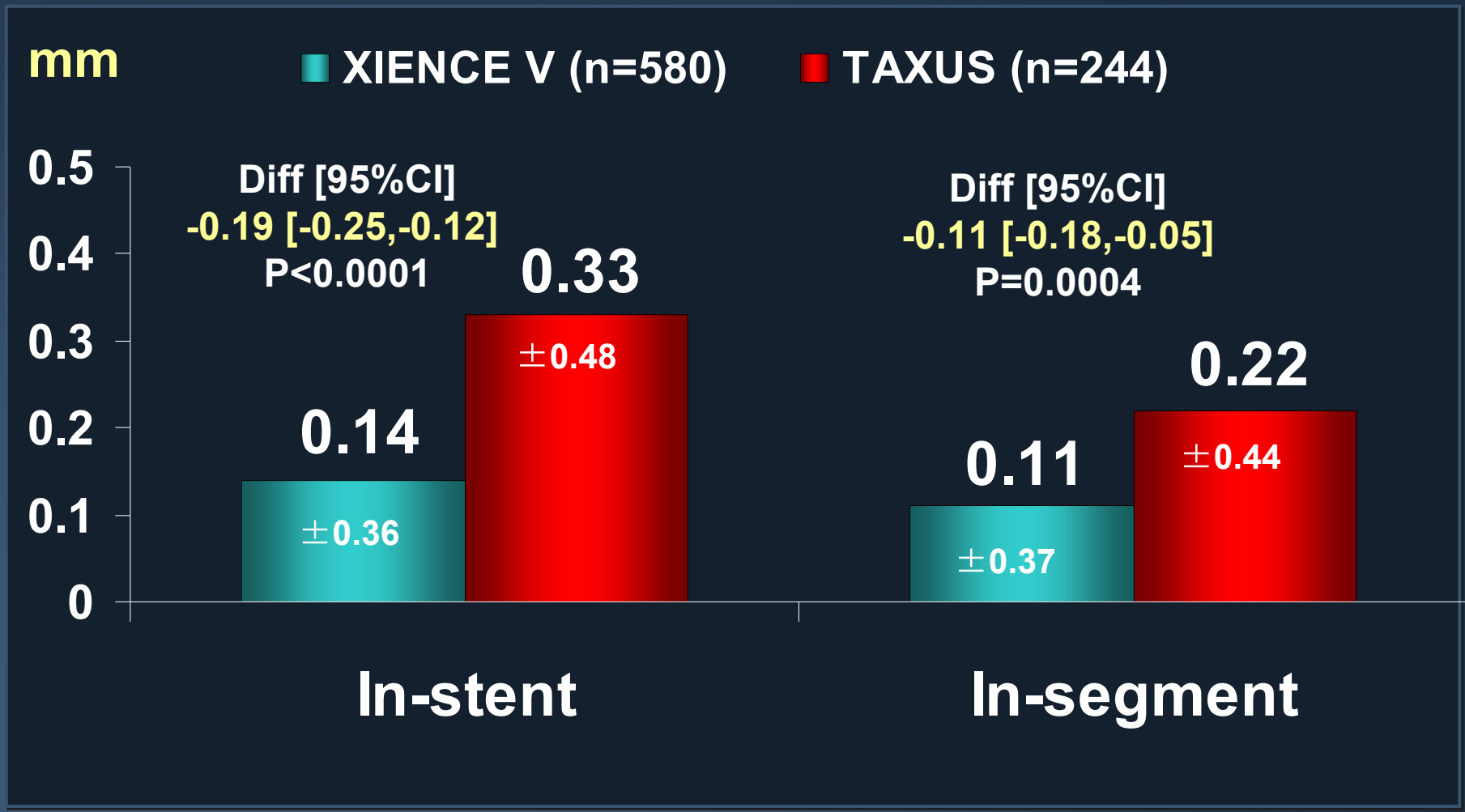
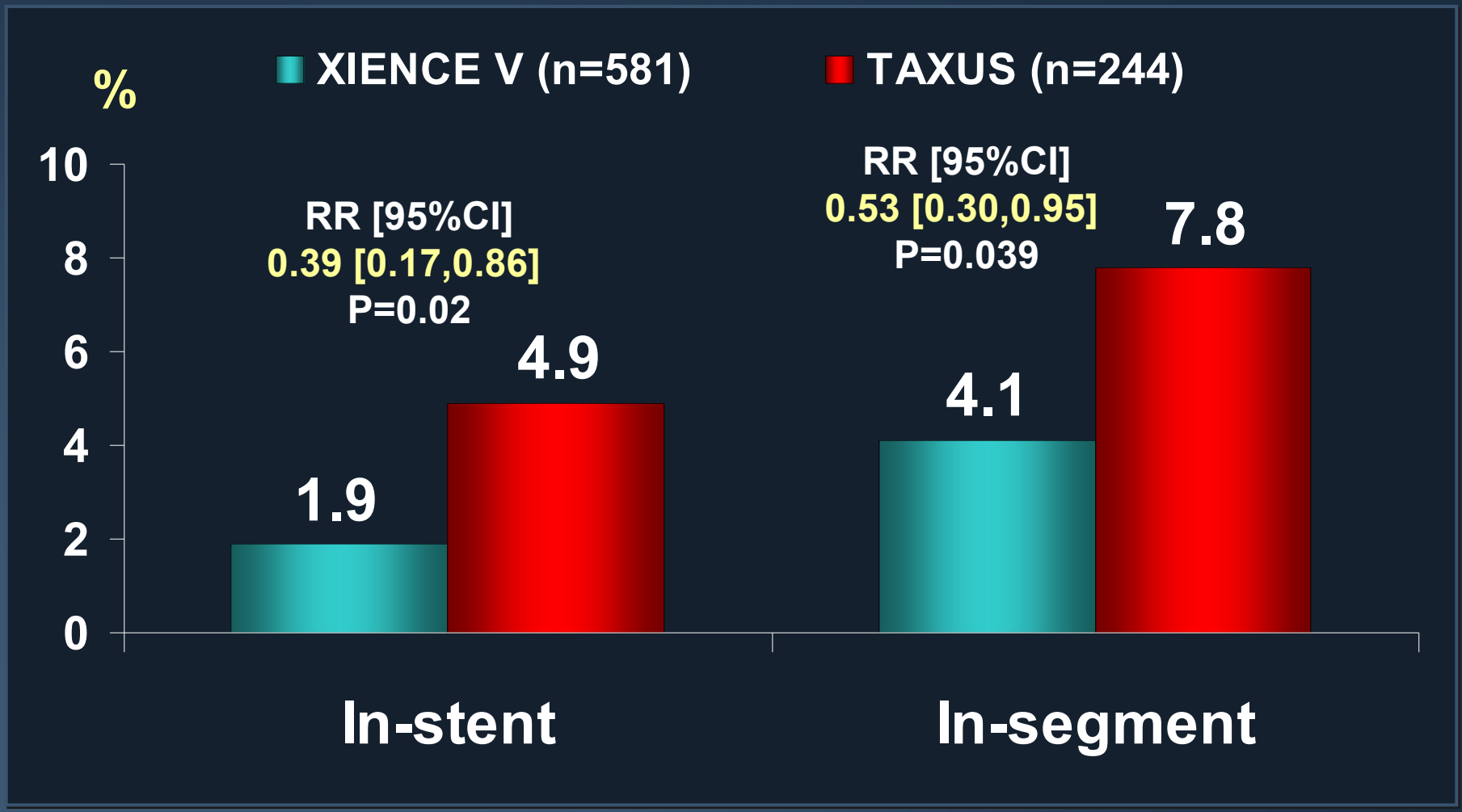
SPIRIT II + III Pooled Meta-analysis

Late Loss



SPIRIT II + III Pooled Meta-analysis

Binary Restenosis



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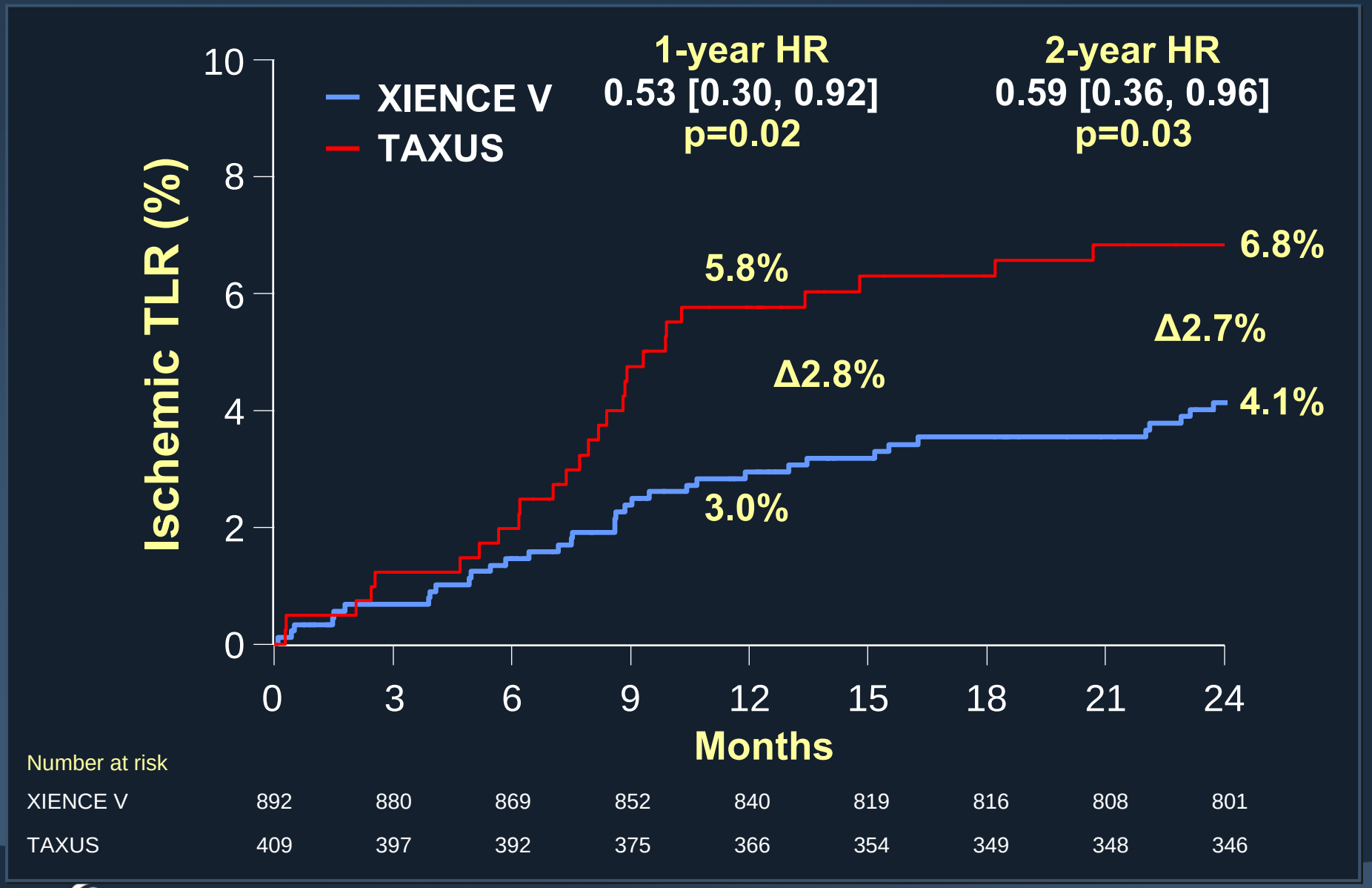
SPIRIT II + III: Ischemic TLR



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SPIRIT II + III Pooled Meta-analysis

Stent Thrombosis

Definition	XIENCE V (N=892)	TAXUS (N=410)	P value
Protocol*			
- Early (0-30 days)	0.3%	0%	
- Late (31 days – 1 year)	0.3%	0.8%	
- Very late (1 – 2 years)	0.5%	0.8%	
- TOTAL	1.2%	1.6%	0.59
ARC Definite/Probable			
- Early (0-30 days)	0.3%	0.2%	
- Late (31 days – 1 year)	0.3%	0.8%	
- Very late (1 – 2 years)	0.5%	0.8%	
- TOTAL	1.2%	1.6%	0.59

*ACS + angio thrombus, or unexplained death or STEMI/Q-wave MI in target lesion distribution w/i 30d

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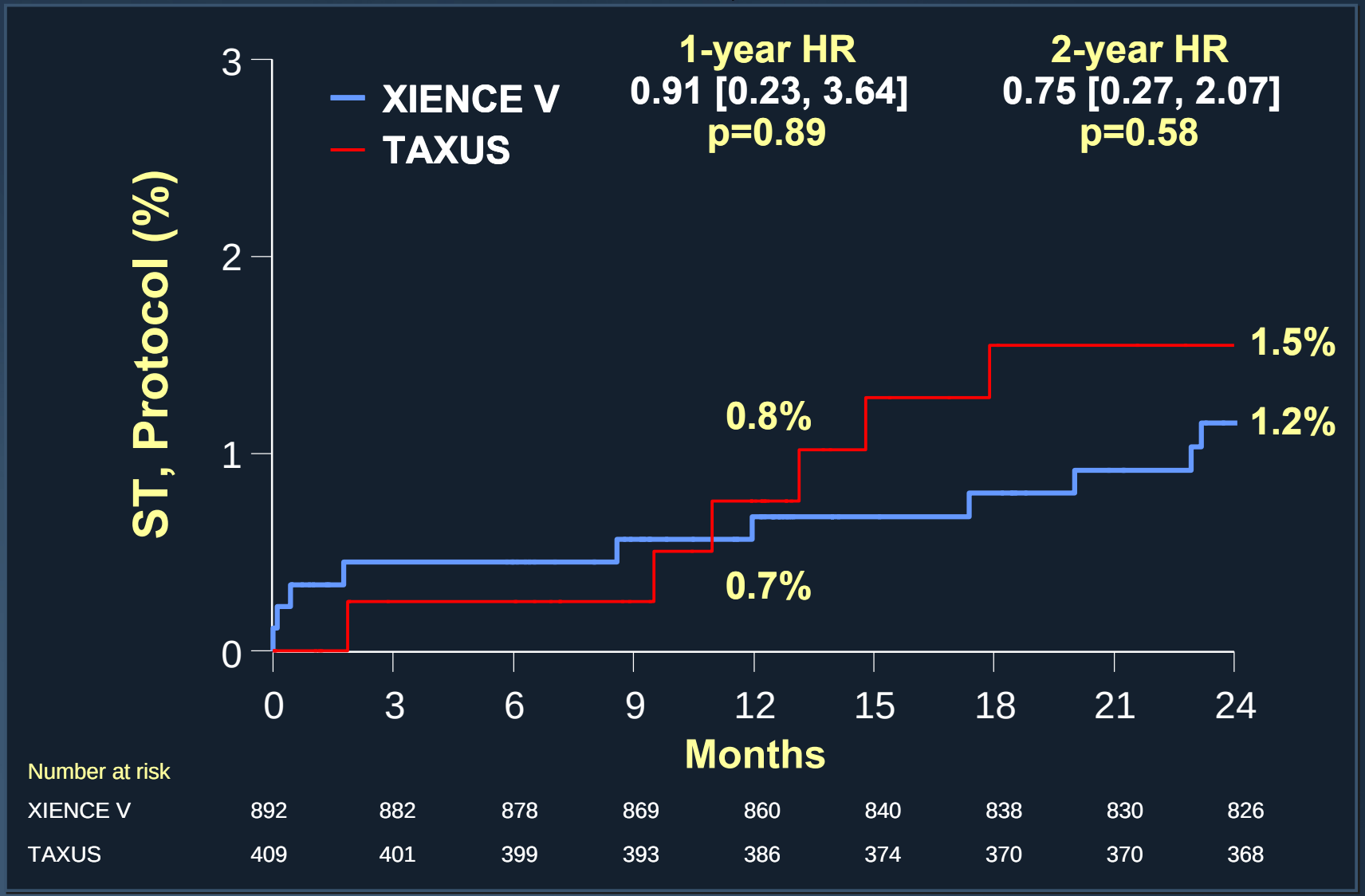
Stent Thrombosis, Protocol Defn.



Protocol definition = ACS + angiographic ST or unexplained death or AMI (STE or Q) in TL distribution w/i 30d

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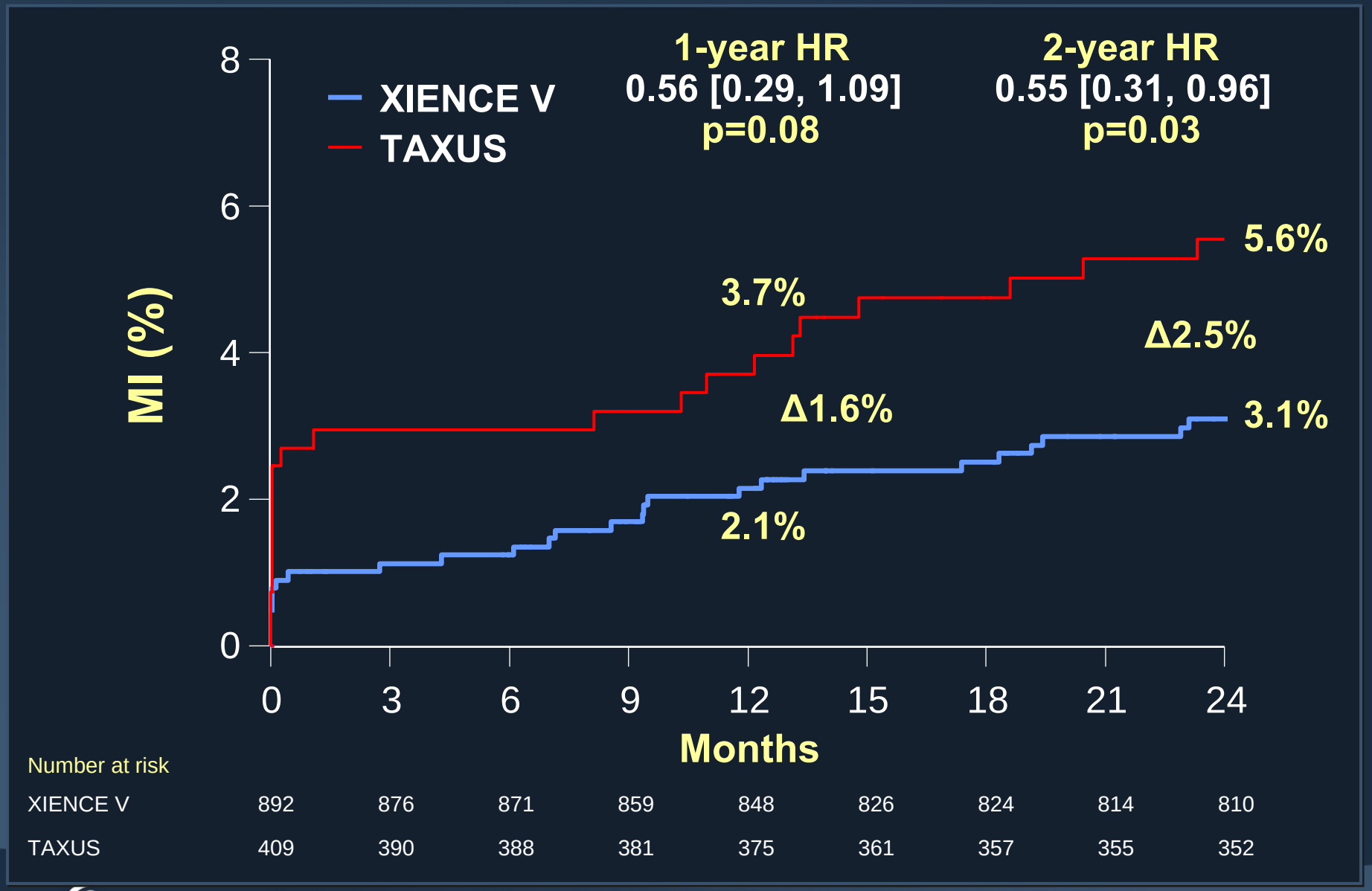
SPIRIT II + III: Myocardial Infarction



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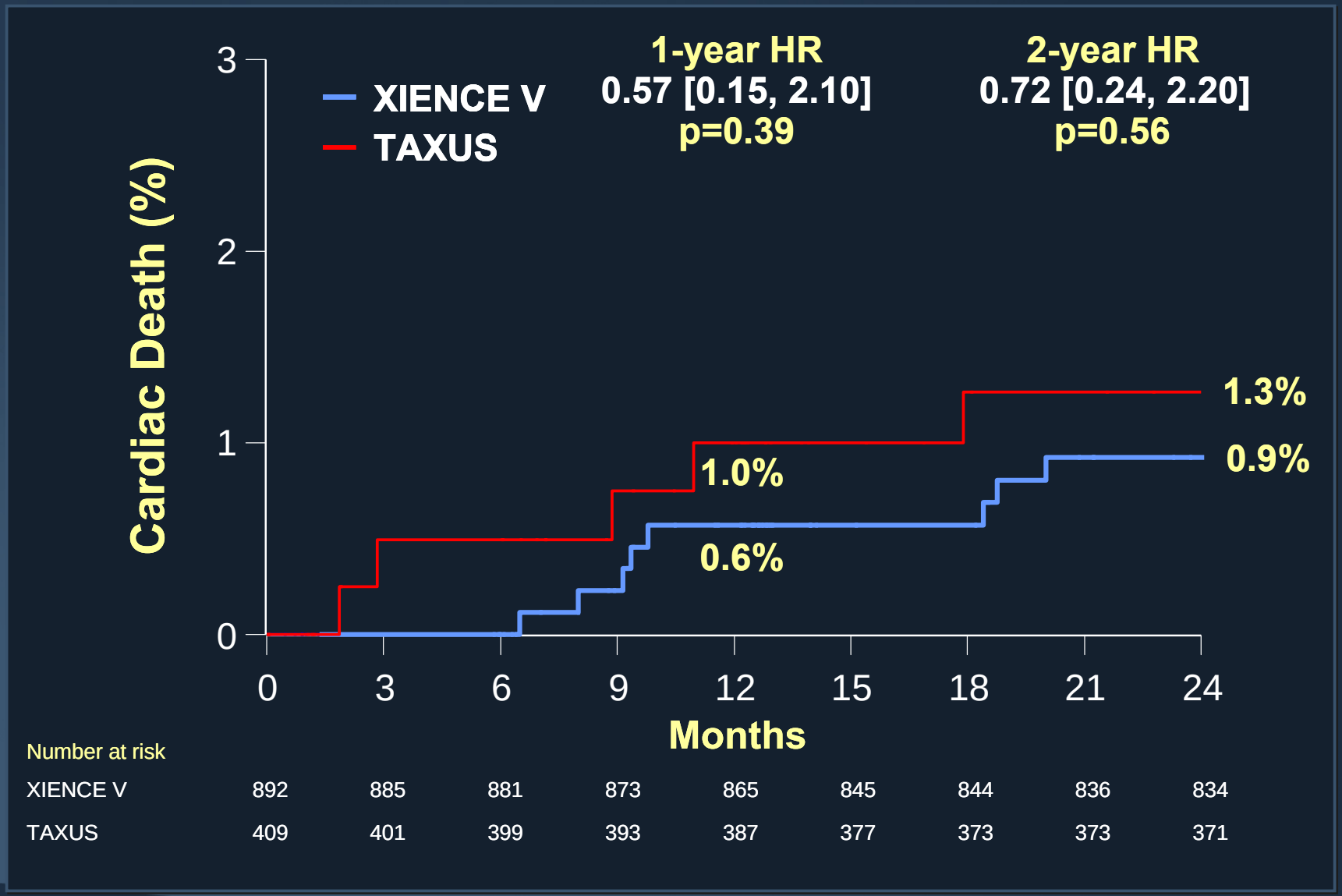
SPIRIT II + III: Cardiac Death



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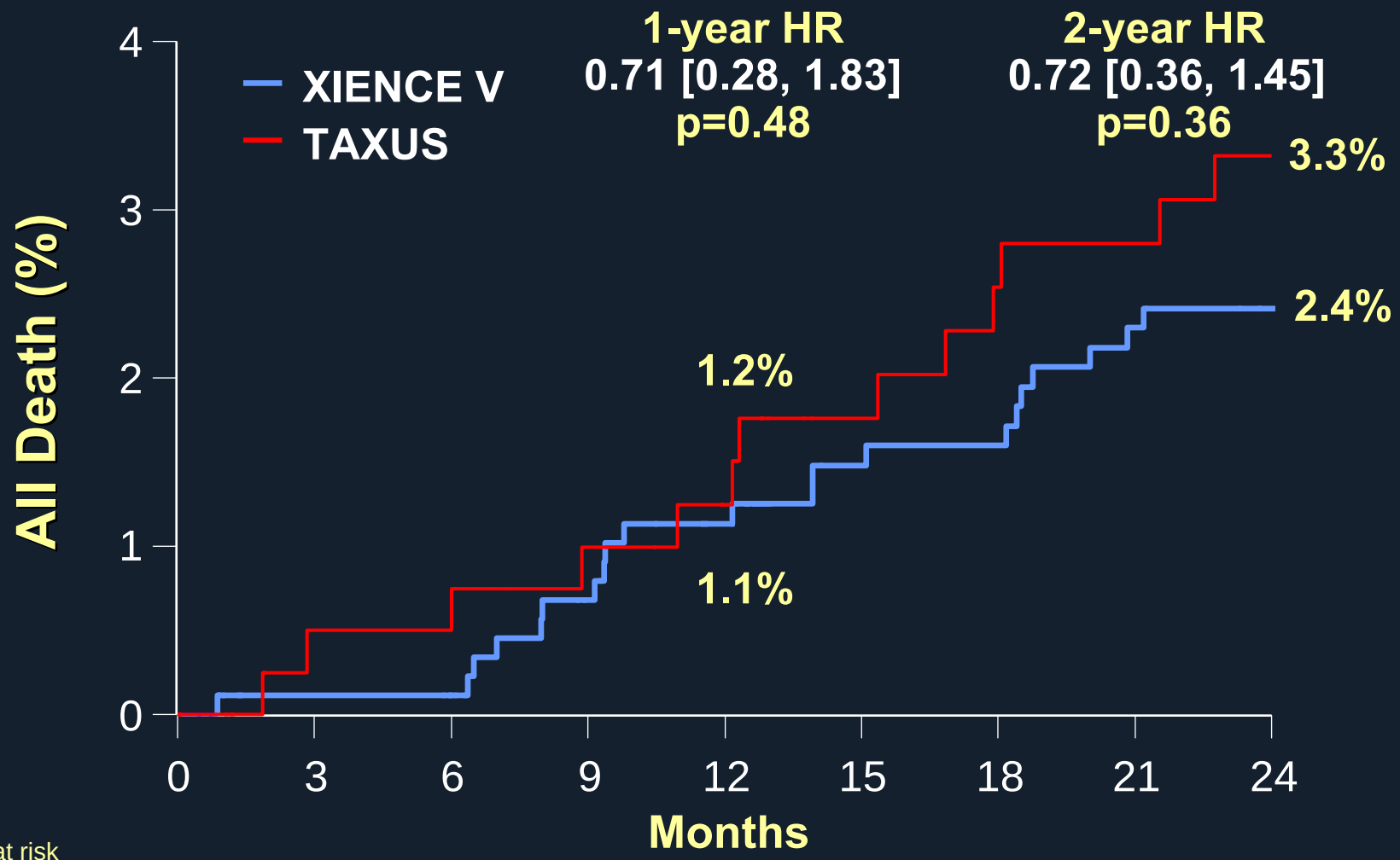
SPIRIT II + III: All Death



Number at risk

XIENCE V	892	885	881	873	865	845	844	836	834
TAXUS	409	401	399	393	387	377	373	373	371

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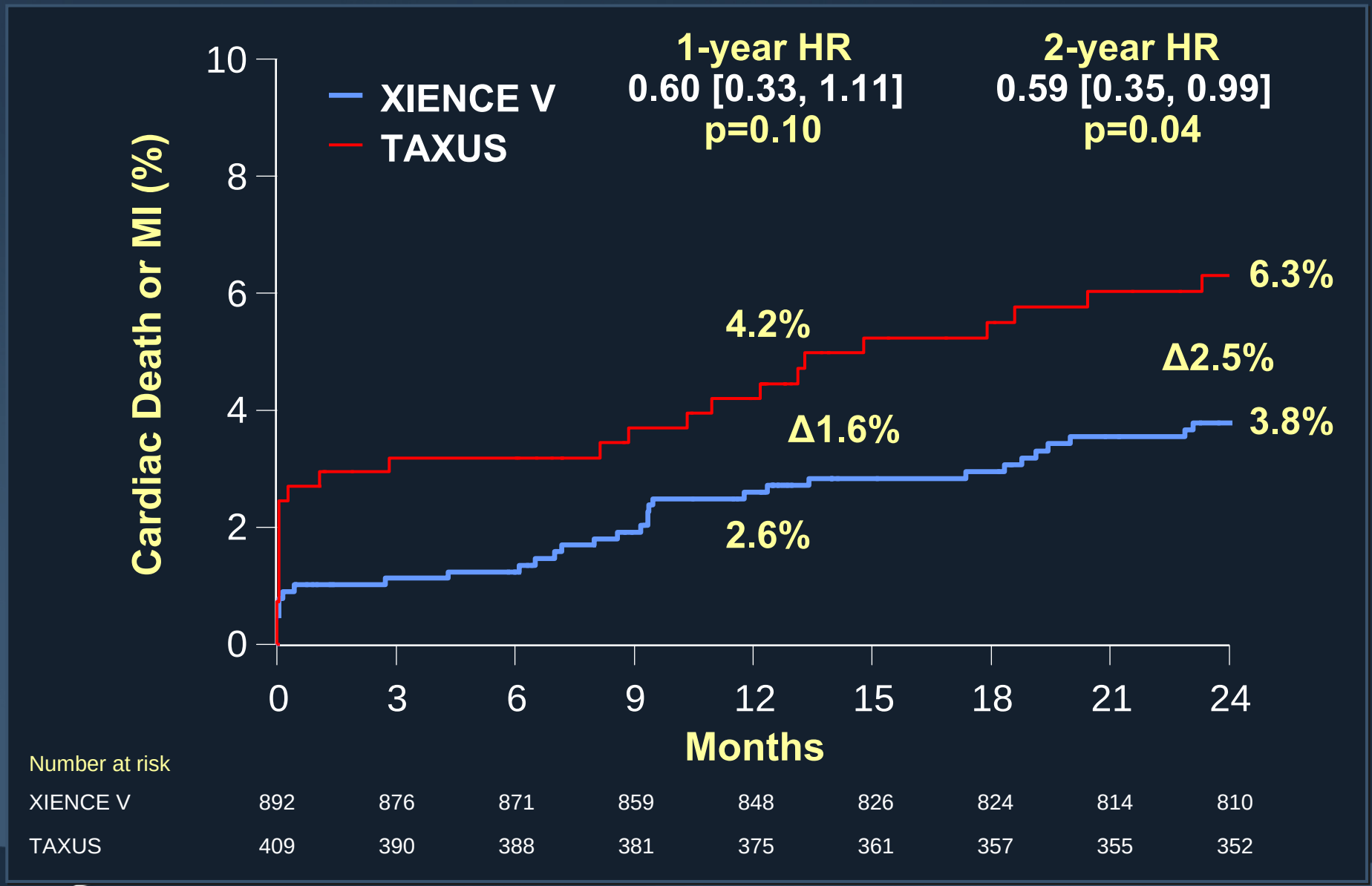
SPIRIT II + III: Cardiac Death or MI



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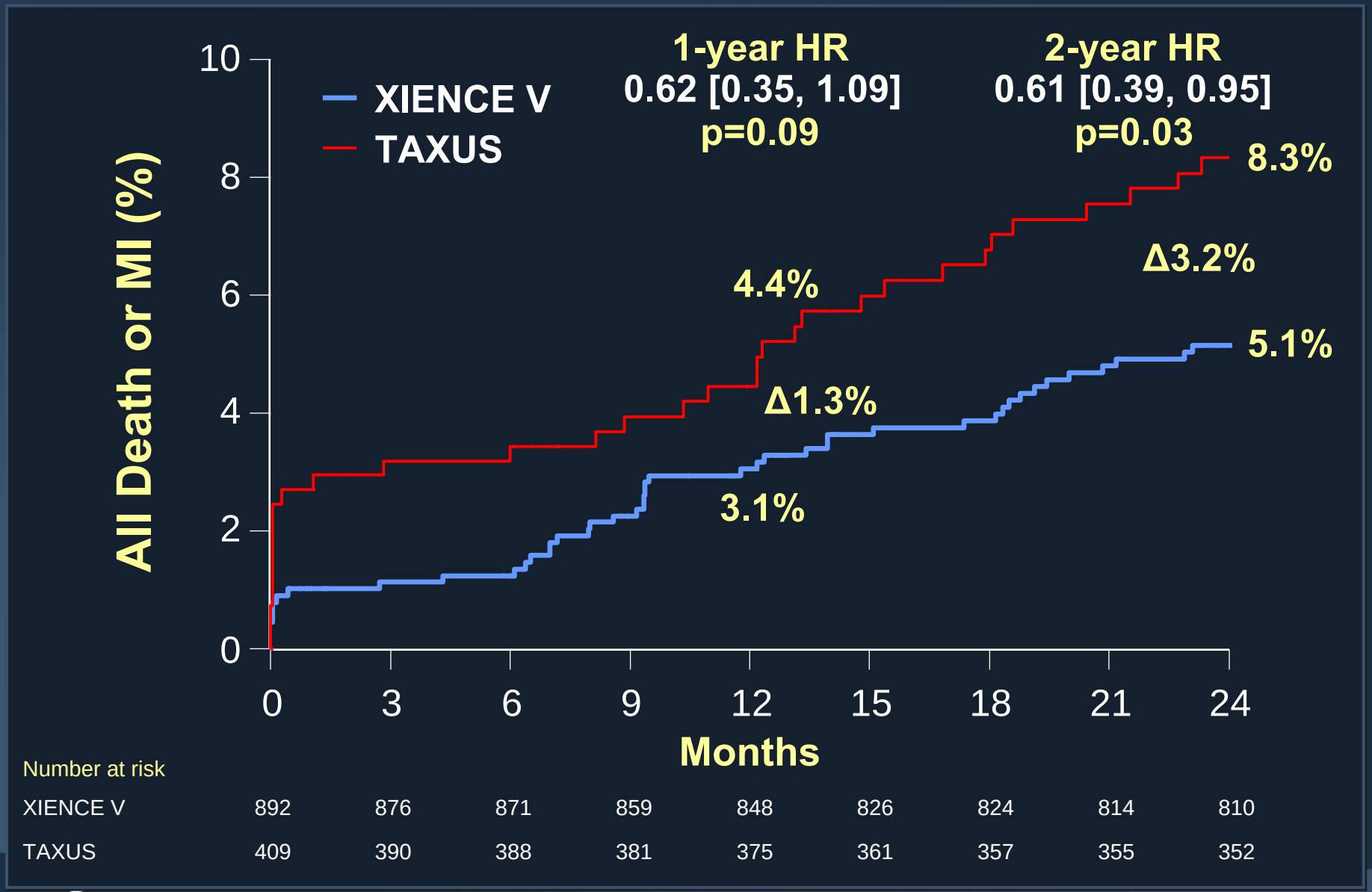
SPIRIT II + III: All Death or MI



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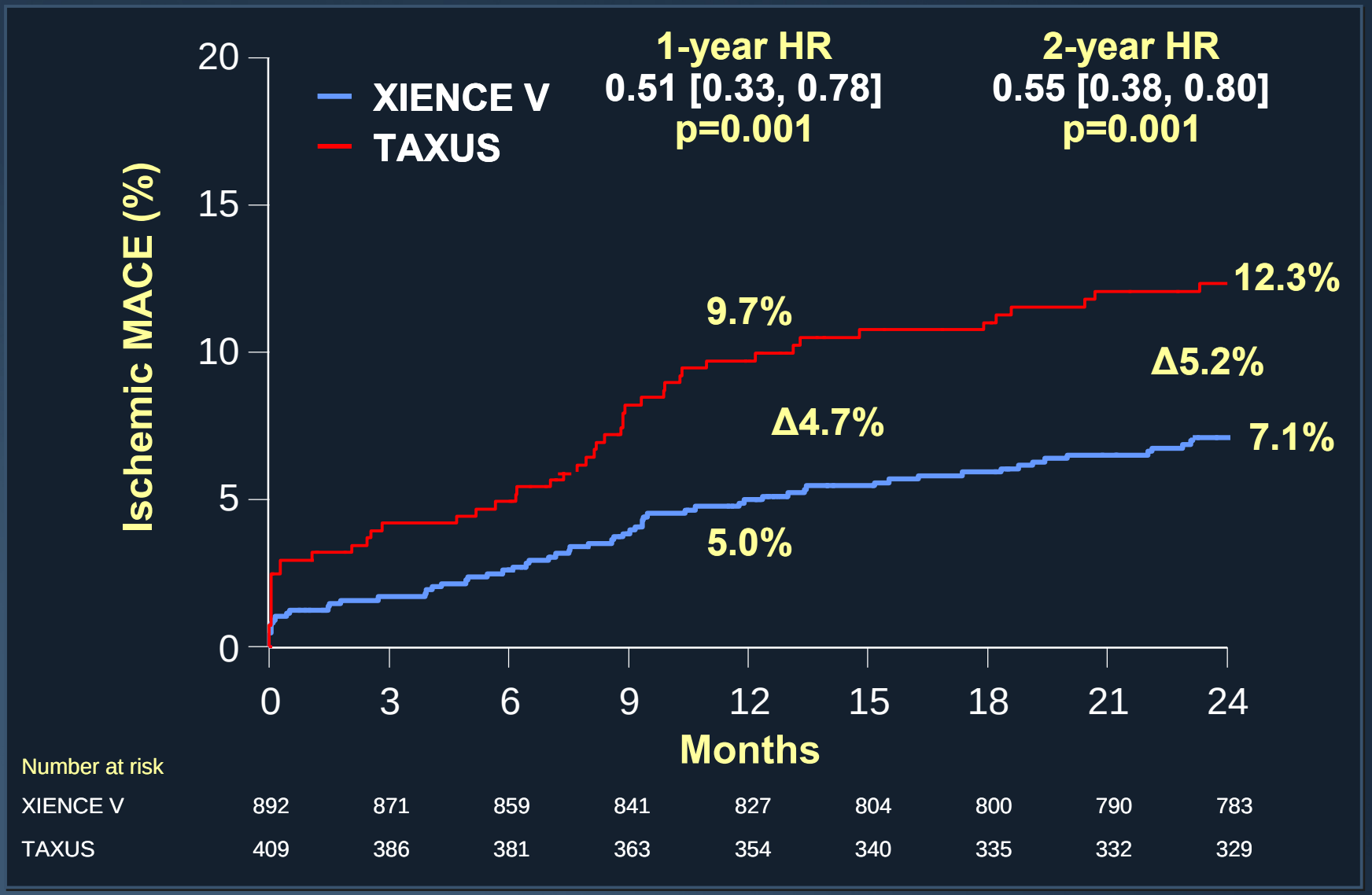
SPIRIT II + III: Ischemic MACE



MACE = Cardiac death, MI, or ischemic TLR

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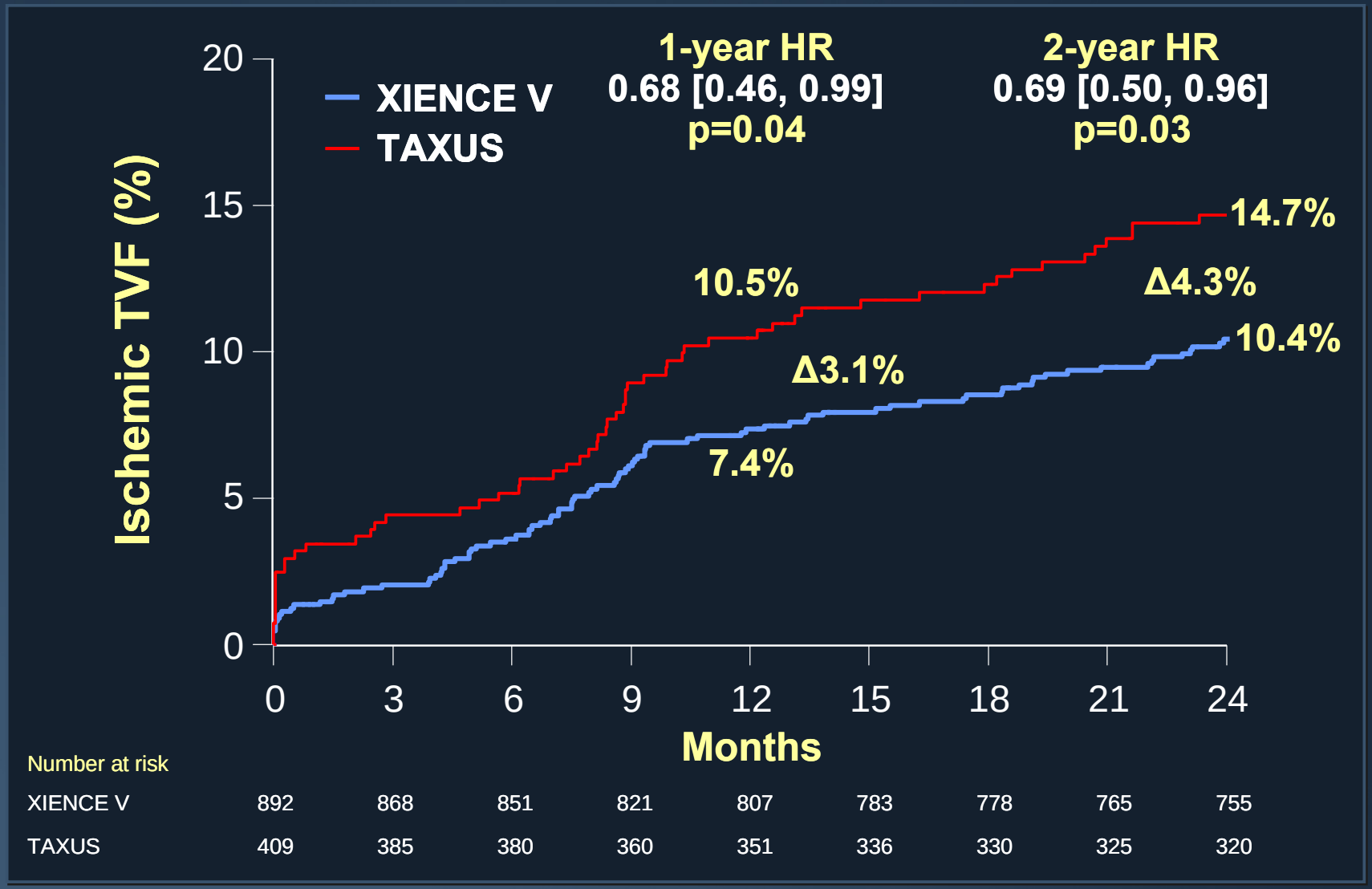
SPIRIT II + III: Ischemic TVF



Ischemic TVF = Cardiac death, MI, or ischemic TVR

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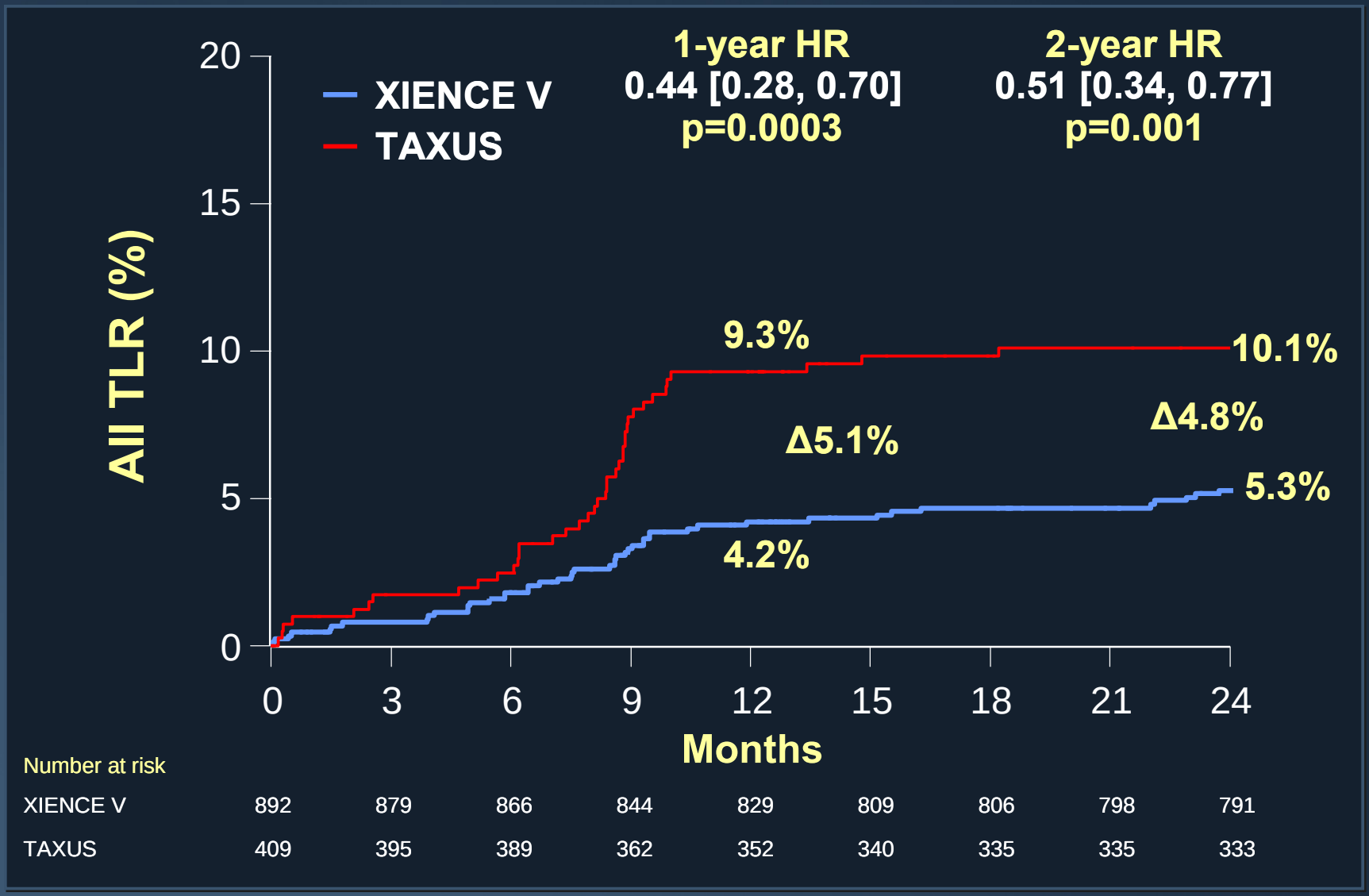
SPIRIT II + III: All TLR



All TLR = Ischemic TLR + non ischemic TLR

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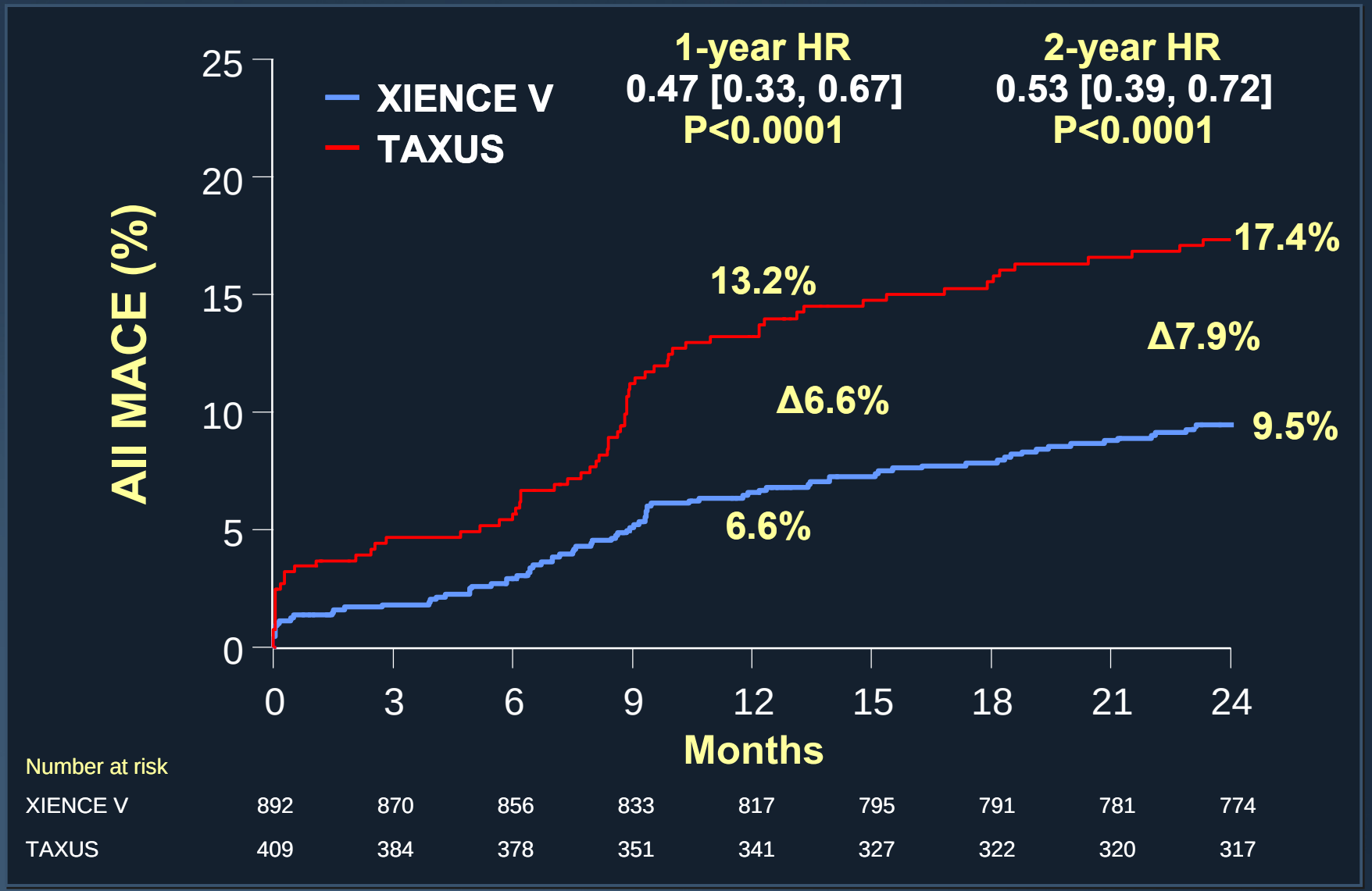
SPIRIT II + III: All MACE



All MACE = All cause death, MI, or all TLR

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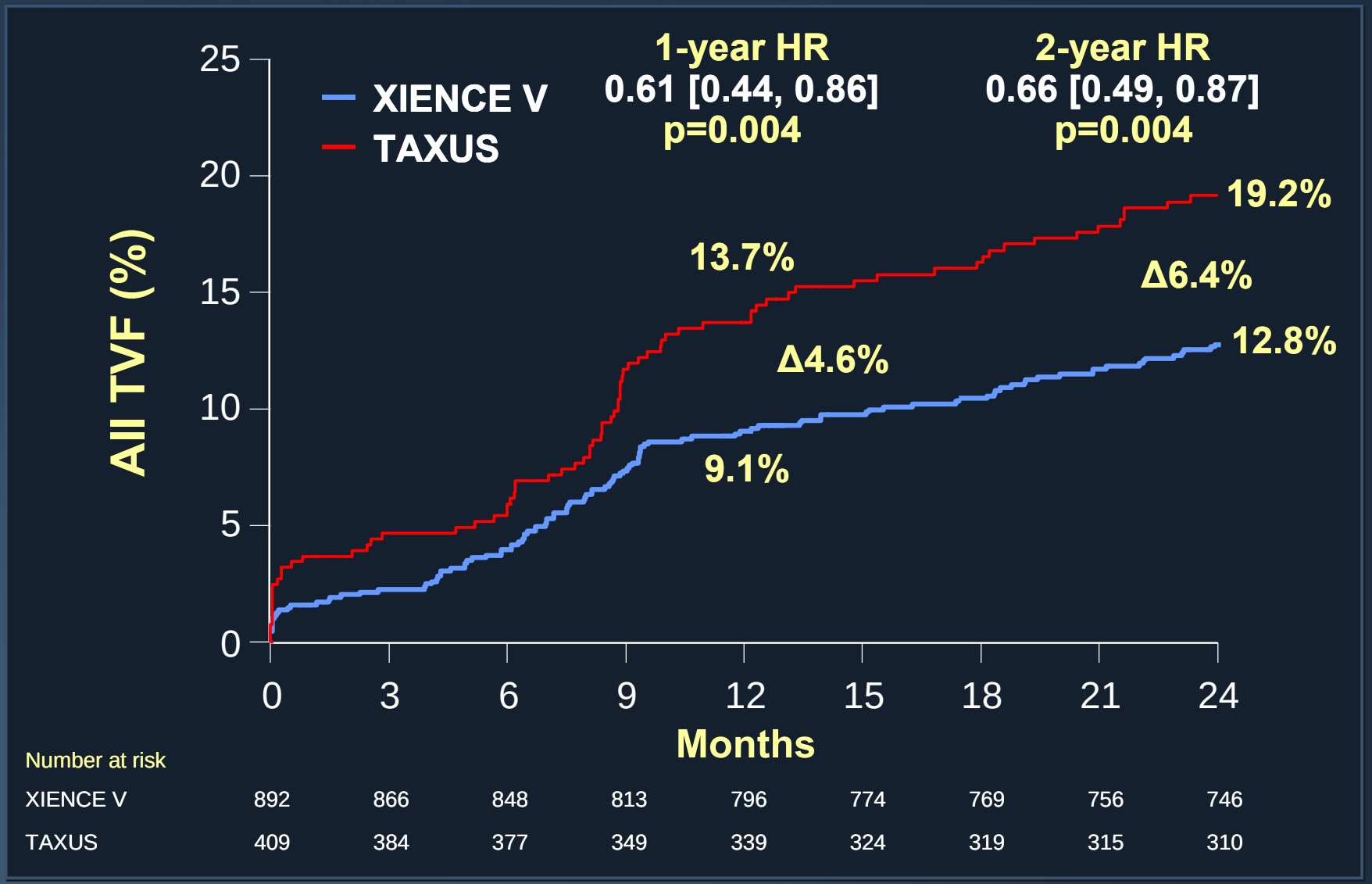
All TVF



TVF = All cause death, MI, or all TVR

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SPIRIT II + III: Subgroups Examined

Angio FU cohort (n=813)

Non Angio FU cohort (n=413)

Age ≥63.0 yrs (n=599)

Age <63.0 yrs (n=627)

Male (n=851)

Female (n=375)

Diabetes (n=377)

No diabetes (n=886)

Single vessel treated (n=1029)

Dual vessel treated (n=197)

RVD >2.765 mm (n=510)

RVD ≤2 .765 mm (n=504)

Lesion length >12.9 mm (n=509)

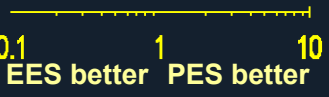
Lesion length ≤12.9 mm (n=503)

Pooled Subgroup Analysis: TVF at 2 Years

Group	EES(%)	PES(%)	Relative Risk (95%CI)	Relative Risk (95%CI)	Probability of Interaction
All randomized (n=1226)	11.0	15.6		0.70 (0.52, 0.95)	-
Angio FU cohort (n=813)	11.6	15.6		0.74 (0.51, 1.07)	0.62
Non Angio FU cohort (n=413)	9.7	15.6		0.62 (0.37, 1.06)	
Age ≥63.0 yrs (n=599)	8.7	16.1		0.54 (0.34, 0.85)	0.14
Age <63.0 yrs (n=627)	13.1	15.1		0.87 (0.57, 1.31)	
Male (n=851)	10.7	13.3		0.81 (0.55, 1.19)	0.25
Female (n=375)	11.5	20.3		0.57 (0.35, 0.92)	
Diabetes (n=337)	14.2	11.3		1.25 (0.66, 2.36)	0.03
No diabetes (n=886)	9.7	17.3		0.56 (0.39, 0.80)	
Single vessel treated (n=1029)	9.5	12.7		0.75 (0.52, 1.09)	0.40
Dual vessel treated (n=197)	18.5	30.6		0.60 (0.36, 1.01)	
RVD >2.765 mm (n=510)	7.8	10.4		0.75 (0.42, 1.33)	0.92
RVD ≤2.765 mm (n=504)	11.3	15.4		0.73 (0.45, 1.17)	
Lesion length >12.9 mm (n=509)	11.2	12.4		0.90 (0.54, 1.50)	0.33
Lesion length ≤12.9 mm (n=503)	7.9	12.8		0.62 (0.36, 1.08)	

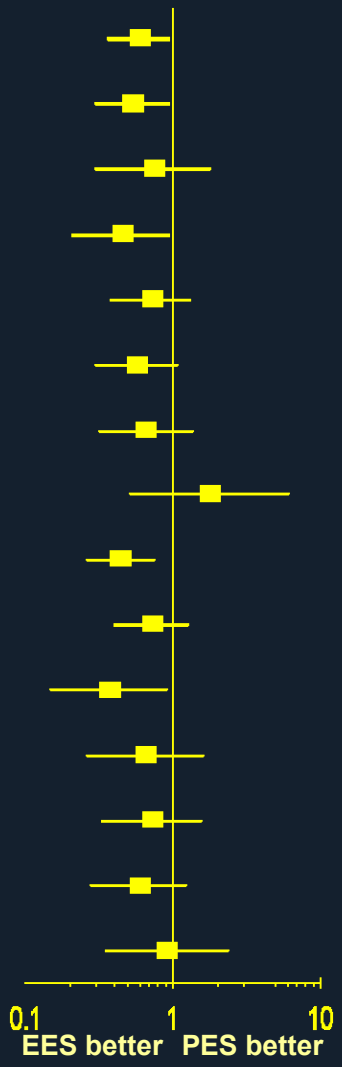
Pooled Subgroup Analysis: MACE at 2 Years

Group	EES(%)	PES(%)	Relative Risk (95%CI)	Relative Risk (95%CI)	Probability of Interaction
All randomized (n=1226)	7.4	13.2		0.56 (0.40, 0.80)	-
Angio FU cohort (n=813)	7.0	13.2		0.53 (0.34, 0.83)	0.69
Non Angio FU cohort (n=413)	8.3	13.3		0.62 (0.35, 1.11)	
Age ≥63.0 yrs (n=599)	6.8	12.9		0.53 (0.31, 0.88)	0.75
Age <63.0 yrs (n=627)	8.0	13.5		0.59 (0.37, 0.96)	
Male (n=851)	6.9	11.4		0.60 (0.38, 0.95)	0.61
Female (n=375)	8.7	17.1		0.51 (0.29, 0.89)	
Diabetes (n=337)	11.3	7.2		1.56 (0.70, 3.46)	0.002
No diabetes (n=886)	5.9	15.5		0.38 (0.25, 0.58)	
Single vessel treated (n=1029)	6.7	9.8		0.69 (0.45, 1.06)	0.06
Dual vessel treated (n=197)	11.1	30.6		0.36 (0.20, 0.66)	
RVD >2.765 mm (n=510)	5.5	7.4		0.74 (0.37, 1.50)	0.66
RVD ≤2.765 mm (n=504)	7.9	12.8		0.62 (0.36, 1.07)	
Lesion length >12.9 mm (n=509)	8.0	9.3		0.86 (0.47, 1.57)	0.29
Lesion length ≤12.9 mm (n=503)	5.4	10.1		0.53 (0.28, 1.02)	



Spirit Pooled Subgroup Analysis: TLR at 2 Years

Group	EES(%)	PES(%)	Relative Risk (95%CI)	Probability of Interaction
All randomized (n=1226)	4.4	7.4	0.59 (0.37, 0.95)	-
Angio FU cohort (n=813)	4.4	8.2	0.53 (0.30, 0.94)	0.55
Non Angio FU cohort (n=413)	4.3	5.9	0.73 (0.30, 1.74)	
Age ≥63.0 yrs (n=599)	3.1	7.0	0.45 (0.21, 0.95)	0.38
Age <63.0 yrs (n=627)	5.5	7.8	0.71 (0.38, 1.32)	
Male (n=851)	3.5	6.3	0.56 (0.30, 1.06)	0.79
Female (n=375)	6.3	9.8	0.65 (0.32, 1.33)	
Diabetes (n=337)	5.4	3.1	1.75 (0.51, 6.01)	0.04
No diabetes (n=886)	3.9	9.0	0.44 (0.26, 0.75)	
Single vessel treated (n=1029)	4.1	5.7	0.71 (0.40, 1.27)	0.20
Dual vessel treated (n=197)	5.9	16.1	0.37 (0.15, 0.89)	
RVD >2.765 mm (n=510)	3.2	4.9	0.65 (0.26, 1.58)	0.88
RVD ≤2.765 mm (n=504)	4.8	6.7	0.71 (0.33, 1.52)	
Lesion length >12.9 mm (n=509)	4.3	7.5	0.58 (0.28, 1.21)	0.45
Lesion length ≤12.9 mm (n=503)	3.7	4.0	0.91 (0.35, 2.35)	



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SPIRIT II + III Pooled Meta-analysis
Conclusions

- Compared to the TAXUS paclitaxel-eluting stent, the XIENCE V everolimus-eluting coronary stent results in:
  - Significantly less TVF and MACE at 2-years, due to significantly lower rates of death or MI and TLR
  - The results were consistent across multiple subgroups examined, except for pts with diabetes in whom outcomes were not significantly different between XIENCE V and TAXUS
    - The small numbers of patients enrolled in these subgroups preclude definitive conclusions

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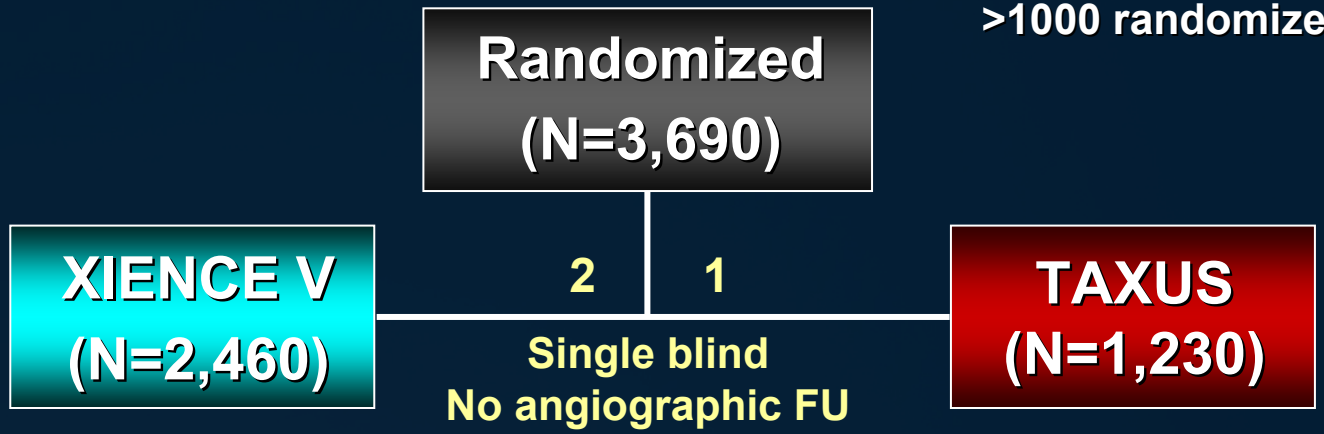
SPIRIT IV Trial

>1000 randomized diabetics



Up to 3 lesions in 1, 2 or 3 separate vessels (2 max per vessel)

Primary endpoint: MACE at 12 months
(cardiac death, MI, ischemia-driven TLR)

Primary Endpoint Results
TCT September 2009
San Francisco

TCT 2009

Current Abbott Vascular Clinical Trials

4 year F/U	2 year F/U	2 year F/U	Enrollment Complete	Enrollment Complete	Enrolling	Enrollment Complete	Enrolling
SPIRIT FIRST	**SPIRIT II**	**SPIRIT III**	**SPIRIT IV**	**SPIRIT V**	**XIENCE V SPIRIT WOMEN**	**XIENCE V USA**	**XIENCE V India**
Safety and Performance	Clinical Support for CE Launch	U.S. and Japan Approval	U.S. Continued Access	Post CE Mark Approval International	Post CE Mark Approval International	U.S. Post Approval	India Post Approval
Europe N=60	International N=300	U.S.: 65 sites Japan: 12 sites N=1380 (1,292/88)	Expanded Enrollment: N=3,690	N=3,000 100 sites Registry N=2,700 Diabetic study N=300	N=2,000 100 sites Registry N=1,550 (1228* pts enrolled) Randomized arm vs Cypher N=450 (37* pts enrolled)	N=~5000	N=1000 Enrolled pts = 600

* As of Dec/2008

Abbott Vascular

Integrated Clinical Program (N > 16,000)

	Pre-approval Clinical Data
SPIRIT FIRST	RCT 1:1 XIENCE V vs. VISION (n = 60) OUS
SPIRIT II	RCT 3:1 XIENCE V vs. TAXUS (n = 300) OUS
SPIRIT III	RCT 2:1 XIENCE V vs. TAXUS (n = 1,002) US
SPIRIT III 4.0	Registry 4.0 mm (n = 80) US
SPIRIT III Japan	Registry (n = 88) Japan

	Ongoing and Planned Clinical Data
SPIRIT IV	RCT XIENCE V vs. TAXUS 2:1 Continued Access (n = 3,690) US
SPIRIT V	Registry (n = 2,700), RCT Diabetics 2:1 vs. TAXUS (n = 300) OUS
XIENCE V SPIRIT Women	Registry (n = 1,550) RCT 2:1 vs. CYPHER (n = 450) OUS
XIENCE V USA	Post-approval Registry – real world (n ~ 5,000) US
XIENCE V India	Post-approval Registry – real world (n = 1,000) OUS

Abbott Vascular

MULTI-LINK VISION® Coronary Stent Systems
Information for Prescribers

℞ ONLY

Table of Contents

Abbott

1.0 DEVICE DESCRIPTION

The MULTI-LINK VISION RX Coronary Stent System and the MULTI-LINK VISION OTW Coronary Stent System (MULTI-LINK VISION Coronary Stent and RX or OTW Delivery System) include:

- A pre-mounted L-605 cobalt chromium alloy (CoCr) (major elements include cobalt, chromium, tungsten, nickel) stent.
- Two radiopaque markers, located underneath the balloon, which fluoroscopically mark the working length of the balloon and the expanded stent length.
- Two proximal delivery system shaft markers (95 cm and 105 cm from the distal tip) that indicate the relative position of the delivery system to the end of a brachial or femoral guiding catheter. Working catheter length is 143 cm.
- For the MULTI-LINK VISION RX Coronary Stent System only, a shaft color change denotes the guide wire exit notch.

Table 1: Device Specifications

Stent Inner Diameter (mm)	Stent Length (mm)	*Minimum Guiding Catheter Compatibility (ID) 5F (0.056" / 1.42 mm)	***in vitro* Stent Nominal Pressure (atm)	Rated Burst Pressure – RBP (atm)	Stent Free % Area
3.0	8, 12, 15, 18, 23, 28	5F	9	16	87
3.5	8, 12, 15, 18, 23, 28	5F	9	16	85
4.0	8, 12, 15, 18, 23, 28	5F	9	16	87

*See Individual manufacturer specifications for (F) equivalent.
Assure full deployment of the stent (see **Clinician Use Information – Deployment Procedure [9.5]). Deployment pressures should be based on lesion characteristics.

2.0 HOW SUPPLIED

Sterile. This device is sterilized with electron beam radiation. Non-pyrogenic. **For one use only. Do not resterilize.** Do not use if the package is open or damaged.

Contents. One (1) MULTI-LINK VISION RX Coronary Stent System or MULTI-LINK VISION OTW Coronary Stent System, One (1) Protective / Regrooming Sheath, One (1) Flushing Tool (for MULTI-LINK VISION RX Coronary Stent System)

Storage. Store in a dry, dark, cool place.

3.0 INDICATIONS

The MULTI-LINK VISION RX and MULTI-LINK VISION OTW Coronary Stent Systems are indicated for improving coronary luminal diameter in the following (see **Individualization of Treatment** [8.1]):

- Patients with symptomatic ischemic heart disease due to discrete *de novo* or restenotic native coronary artery lesions (length ≤ 25 mm) with reference vessel diameters ranging from 3.0 mm to 4.0 mm.

- Patients with symptomatic ischemic heart disease due to lesions in saphenous vein bypass grafts (length ≤ 25 mm) with reference vessel diameters ranging from 3.0 mm to 4.0 mm.

- Restoring coronary flow in patients experiencing acute myocardial infarction, as confirmed by ST segment elevation or angiographic findings, who present within 12 hours of symptom onset with native coronary artery lesions of length ≤ 25 mm with a reference vessel diameter of 3.0 mm to 4.0 mm.

- Outcome (beyond 9 months) for this permanent implant is unknown at present.

4.0 CONTRAINDICATIONS

The MULTI-LINK VISION RX and MULTI-LINK VISION OTW Coronary Stent Systems are contraindicated for use in:

- Patients in whom antiplatelet and / or anticoagulant therapy is contraindicated.

- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon.

5.0 WARNINGS AND PRECAUTIONS

(See **Individualization of Treatment** [8.1].)

WARNINGS

- Judicious selection of patients is necessary since the use of this device carries the associated risk of subacute thrombosis, vascular complications and / or bleeding events.

- Persons allergic to L-605 cobalt chromium alloy (including the major elements cobalt, chromium, tungsten, nickel) may suffer an allergic reaction to this implant.

- Implantation of the stent should be performed only by physicians who have received appropriate training.

- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.

- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of endothelialized stents is unknown at present.

- When multiple stents are required, stent materials should be of similar composition. Placing multiple stents of different metals in contact with each other may increase the potential for corrosion. The risk of *in vivo* corrosion does not appear to increase based on *in vitro* corrosion tests using an L-605 CoCr alloy stent (MULTI-LINK VISION Coronary Stent) in combination with a 316L stainless steel alloy stent (MULTI-LINK TETRA Coronary Stent).

5.1 Stent Handling – Precautions

- **For single use only.** Do not resterilize or reuse. Note the product "Use By" date.
- **Do not remove stent from its delivery system** as removal may damage the stent and / or lead to stent embolization. Stent system is intended to perform as a system.
- Delivery system should not be used in conjunction with other stents.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important during catheter removal from packaging, placement over guide wire and advancement through rotating hemostatic valve adapter and guiding catheter hub.
- Do not manipulate (e.g., “roll") the stent with your fingers, as this action may loosen the stent from the delivery balloon.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

5.2 Stent Placement – Precautions

- **Do not prepare or pre-inflate delivery system prior to stent deployment** other than as directed. Use balloon purging technique described in **Delivery System Preparation** (9.3.2).
- Implanting a stent may lead to dissection of the vessel distal and / or proximal to the stent and may cause acute closure of the vessel requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent in placement of the distal stent and reduces the chances for dislodging the proximal stent.
- Do not expand the stent if it is not properly positioned in the vessel. (See **Stent / System Removal – Precautions** [5.3].
- Placement of a stent has the potential to compromise side branch patency.
- **Do not exceed Rated Burst Pressure (RBP) as indicated on product label.** Balloon pressures should be monitored during inflation. Use of pressures higher than specified on product label may result in a ruptured balloon with possible intimal damage and dissection.

- An unexpanded stent may be retracted into the guiding catheter one time only. Subsequent movement in and out through the distal end of the guiding catheter should not be performed as the stent may be damaged when retracting the undeployed stent back into the guiding catheter. Should **any resistance** be felt **at any time** during withdrawal of the coronary stent system, the entire system should be **removed as a single unit**.

- Stent retrieval methods (use of additional wires, snares and / or forceps) may result in additional trauma to the coronary vasculature and / or the vascular access site. Complications may include bleeding, hematoma or pseudoaneurysm.

5.3 Stent / System Removal – Precautions

Should **any resistance** be felt **at any time** during either lesion access or removal of the delivery system post-stent implantation, the entire system should be **removed as a single unit**.

When removing the delivery system as a single unit:

- DO NOT retract the delivery system into the guiding catheter.
- Position the proximal balloon marker just distal to the tip of the guiding catheter.
- Advance the guide wire into the coronary anatomy as far distally as safely possible.
- Tighten the rotating hemostatic valve to secure the delivery system to the guiding catheter; then remove the guiding catheter and delivery system as a **single unit**.

Failure to follow these steps and / or applying excessive force to the delivery system can potentially result in loss or damage to the stent and / or delivery system components.

If it is necessary to retain guide wire position for subsequent artery / lesion access, leave the guide wire in place and remove all other system components.

5.4 Post Implant – Precautions

Care must be exercised when **crossing a newly deployed stent** with a coronary guide wire, balloon or delivery system to avoid disrupting the stent geometry.

5.4.1 MRI Statement

The MULTI-LINK VISION Coronary Stent has been shown in non-clinical testing to be MRI safe immediately following implantation. **MRI test conditions used to evaluate this stent were: for magnetic field interactions, a static magnetic field strength of 3 tesla with a maximum spatial gradient magnetic field of 3.3 tesla/meter; for MRI-related heating, a maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of MR imaging.** While a single stent produced a temperature rise of less than 0.6°C and should not migrate under these conditions, the response of overlapping stents or stents with fractured struts is unknown. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than 3 tesla. MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

6.0 ADVERSE EVENTS

6.1 Observed Adverse Events

Observed adverse event experience for the Guidant MULTI-LINK VISION Coronary Stent was obtained in the VISION Registry. See Section 7 – **CLINICAL STUDIES** for more complete descriptions of the study design and results.

6.1.1 VISION Registry – de novo Lesions

The VISION Registry was a multi-center, non-randomized, prospective study conducted to assess the safety and efficacy of the Guidant MULTI-LINK VISION RX Coronary Stent System in native *de novo* coronary artery lesions in 267 patients. The primary endpoint was target vessel failure (TVF) at 180 days defined as a composite of death, Q-Wave Myocardial Infarction (QMI), non-Q-Wave Myocardial Infarction (non-QMI), Target Site Revascularization (TSR) or Target Vessel Revascularization (TVR) by Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI). Secondary endpoints of MACE and in-hospital TVF at 270 days were also evaluated. These results were compared to results of the 202 *de novo* lesion patients treated with the Guidant MULTI-LINK RX TETRA Coronary Stent System in the TETRA Registry.

A total of 297 Guidant MULTI-LINK VISION Coronary Stents were implanted in 267 patients. For the 180-day time point, there were three (1.2%) deaths, two (0.8%) Q-Wave MIs, two (0.8%) non Q-Wave MIs, 13 (5.0%) TSR by PCI, 0 (0.0%) TSR by CABG, one (0.4%) Subacute Thrombosis, three (1.2%) cerebrovascular accidents, six (2.3%) serious bleeding events, and four (1.6%) serious vascular events.

There were two (0.8%) device malfunctions reported in the VISION Registry: inability to cross the lesion on the first attempt and inaccurate stent placement. These two device malfunctions did not result in adverse events. There was one stent delivery failure that resulted in the stent being lost in the peripheral system. The patient suffered no adverse events and a subsequent Guidant MULTI-LINK VISION Coronary Stent was successfully deployed.

Table 2 summarizes the Principal Adverse Events of patients receiving the Guidant MULTI-LINK VISION RX Coronary Stent System at 180 and 270 days, along with those receiving the Guidant MULTI-LINK TETRA Coronary Stent System at 180 days.

Table 2: VISION Registry – Principal Adverse Events through 180 & 270 Days

% [95% confidence interval] (number)

180-Day Comparison - *de novo* Registries			270-Day Data
Complication	MULTI-LINK VISION (N = 267)[1]	MULTI-LINK TETRA (N = 202)	MULTI-LINK VISION (N = 267)[1]
Any Adverse Event	**13.2%** [9.3%, 17.9%] (34)	**20.9%** [15.4%, 27.3%] (41)	**20.5%** [15.7%, 25.9%] (53)
Early (In-Hospital)	**5.0%** [2.7%, 8.5%] (13)	**7.9%** [4.6%, 12.5%] (16)	**5.0%** [2.7%, 8.4%] (13)
Out-of-Hospital	**8.5%** [5.4%, 12.6%] (22)	**12.8%** [8.4%, 18.3%] (25)	**15.8%** [11.6%, 20.9%] (41)
Death Total	**1.2%** [0.2%, 3.4%] (3)	**0.5%** [0.0%, 2.8%] (1)	**1.2%** [0.2%, 3.3%] (3)
Early (In-Hospital)	**0.4%** [0.0%, 2.1%] (1)	**0%** [0.0%, 1.8%] (0)	**0.4%** [0.0%, 2.1%] (1)
Out-of-Hospital	**0.8%** [0.1%, 2.8%] (2)	**0.5%** [0.0%, 2.8%] (1)	**0.8%** [0.1%, 2.8%] (2)
QMI Total	**0.8%** [0.1%, 2.8%] (2)	**0%** [0.0%, 1.9%] (0)	**0.8%** [0.1%, 2.8%] (2)
Early (In-Hospital)	**0.4%** [0.0%, 2.1%] (1)	**0%** [0.0%, 1.8%] (0)	**0.4%** [0.0%, 2.1%] (1)
Out-of-Hospital	**0.4%** [0.0%, 2.1%] (1)	**0%** [0.0%, 1.9%] (0)	**0.4%** [0.0%, 2.1%] (1)
Non-Q MI Total	**0.8%** [0.1%, 2.8%] (2)	**2.6%** [0.8%, 5.9%] (5)	**0.8%** [0.1%, 2.8%] (2)
Early (In-Hospital)	**0.8%** [0.1%, 2.8%] (2)	**2.0%** [0.5%, 5.0%] (4)	**0.8%** [0.1%, 2.8%] (2)
Out-of-Hospital	**0%** [0.0%, 1.4%] (0)	**0.5%** [0.0%, 2.8%] (1)	**0%** [0.0%, 1.4%] (0)
TSR CABG Total	**0%** [0.0%, 1.4%] (0)	**1.0%** [0.1%, 3.6%] (2)	**0.4%** [0.0%, 2.1%] (1)
Early (In-Hospital)	**0%** [0.0%, 1.4%] (0)	**0%** [0.0%, 1.8%] (0)	**0%** [0.0%, 1.4%] (0)
Out-of-Hospital	**0%** [0.0%, 1.4%] (0)	**1.0%** [0.1%, 3.6%] (2)	**0.4%** [0.0%, 2.1%] (1)
TSR PCI Total	**5.0%** [2.7%, 8.5%] (13)	**8.7%** [5.1%, 13.5%] (17)	**11.2%** [7.6%, 15.7%] (29)
Early (In-Hospital)	**0.8%** [0.1%, 2.8%] (2)	**0%** [0.0%, 1.8%] (0)	**0.8%** [0.1%, 2.8%] (2)
Out-of-Hospital	**4.7%** [2.4%, 8.0%] (12)	**8.7%** [5.1%, 13.5%] (17)	**10.8%** [7.3%, 15.2%] (28)
*SAT Total	**0.4%** [0.0%, 2.1%] (1)	**0%** [0.0%, 1.9%] (0)	**0.4%** [0.0%, 2.1%] (1)
Early (In-Hospital)	**0.4%** [0.0%, 2.1%] (1)	**0%** [0.0%, 1.8%] (0)	**0.4%** [0.0%, 2.1%] (1)
Out-of-Hospital	**0%** [0.0%, 1.4%] (0)	**0%** [0.0%, 1.9%] (0)	**0%** [0.0%, 1.4%] (0)
*Cerebrovascular Accident Total	**1.2%** [0.2%, 3.4%] (3)	**0.5%** [0.0%, 2.8%] (1)	**1.2%** [0.2%, 3.3%] (3)
Early (In-Hospital)	**0.4%** [0.0%, 2.1%] (1)	**0%** [0.0%, 1.8%] (0)	**0.4%** [0.0%, 2.1%] (1)
Out-of-Hospital	**0.8%** [0.1%, 2.8%] (2)	**0.5%** [0.0%, 2.8%] (1)	**0.8%** [0.1%, 2.8%] (2)
*Bleeding Complications Total	**2.3%** [0.9%, 5.0%] (6)	**3.1%** [1.1%, 6.5%] (6)	**2.7%** [1.1%, 5.5%] (7)
Early (In-Hospital)	**0.8%** [0.1%, 2.8%] (2)	**3.0%** [1.1%, 6.4%] (6)	**0.8%** [0.1%, 2.8%] (2)
Out-of-Hospital	**1.6%** [0.4%, 3.9%] (4)	**0%** [0.0%, 1.9%] (0)	**1.9%** [0.6%, 4.4%] (5)
*Vascular Complications Total	**1.6%** [0.4%, 3.9%] (4)	**4.6%** [2.1%, 8.5%] (9)	**1.9%** [0.6%, 4.4%] (5)
Early (In-Hospital)	**1.2%** [0.2%, 3.4%] (3)	**3.0%** [1.1%, 6.4%] (6)	**1.2%** [0.2%, 3.3%] (3)
Out-of-Hospital	**0.4%** [0.0%, 2.1%] (1)	**1.5%** [0.3%, 4.4%] (3)	**0.8%** [0.1%, 2.8%] (2)
Stent Delivery Failure	**0.4%** [0.0%, 2.1%] (1)	**0.5%** [0.0%, 2.7%] (1)	**0.4%** [0.0%, 2.1%] (1)

[1]268 patients enrolled but patient 306-4002 is excluded due to MULTI-LINK VISION stent being implanted in SVG, so n = 267.

- *Secondary endpoints were analyzed on per protocol evaluable patients. There were n = 258 patients available at the 180 day f/u time point and there were n = 259 patients available at the 270 day f/u time point.
- Any Adverse event includes death, Q-Wave MI, non-Q-Wave MI, TSR CABG, TSR PCI, SAT, cerebrovascular accident, serious bleeding event, and serious vascular event.
- Early (In-Hospital) refers to events during the hospitalization for stent placement. If the patient had a prolonged hospitalization, in-hospitalization was considered to be less than or equal to 7 days post-procedure.
- In cases where a patient experienced both an In-Hospital and an Out-of-Hospital event, they are counted once in each group, however they are counted only once in the total patients for that category. Hence, the sum of the In-Hospital and Out-of Hospital rate may not equal the total rate.
- See Table 5 footnotes for additional VISION Registry definitions.

6.1.2 REVIVE Study – Saphenous Vein Bypass Grafts

Guidant MULTI-LINK DUET RX Coronary Stent System

Based on equivalency in *de novo* lesions and the similarities in design and manufacture of the Guidant MULTI-LINK DUET Coronary Stent Systems, the following study data demonstrates suitability of the Guidant MULTI-LINK VISION Coronary Stent System for use in saphenous vein bypass grafts.

The REVIVE Study was a multi-center, non-randomized, prospective, consecutive enrollment study conducted in 22 US centers that included 160 patients with saphenous vein bypass graft lesions. The primary endpoint of Target Vessel Failure (TVF) at six months post-index procedure was defined as the composite of death, Q-Wave MI, non-Q-Wave MI and revascularization by CABG or PTCA attributable to the target vessel. An independent Clinical Events Committee adjudicated all MACE.

At 30 days post-procedure, death occurred in three (1.9%) patients, 12 patients suffered non-Q-Wave MI (7.5%) and one patient experienced Q-Wave MI (0.6%). Two patients (1.3%) underwent CABG for TSR, and one (0.6%) underwent CABG for TVR. No patients experienced subacute (stent) thrombus. Bleeding complications occurred in four (2.5%) patients, four (2.5 %) had vascular complications and two (1.3%) of the patients experienced a CVA.

The 180-day MACE rate of the REVIVE Study patients was 19.4% (n = 31). Evaluating the combined In- and Out-of-Hospital events to 180 days post-procedure, there were five (3.1%) deaths, one (0.6%) Q-Wave MI and 17 (10.6%) patients experienced non-Q-Wave MI. Six (3.8%) patients required CABG and 12 (7.5%) underwent PTCA (18 total revascularization procedures; 11.3%). No patients experienced stent thrombosis, six (3.8%) had bleeding complications, five (3.1%) had vascular complications and three (1.9%) experienced a CVA.

Table 3 summarizes the Principal Adverse Events of patients receiving the Guidant MULTI-LINK DUET RX Coronary Stent System in saphenous vein bypass graft lesions (REVIVE Study) through 180-day follow-up.

Table 3: REVIVE Study – Principal Adverse Events through 180 Days

% [95% confidence interval] (number)

Complication	DUET REVIVE Study – SVG (n = 160)	DUET Study – *de novo* (n = 270)
Any Adverse Event Early (In-Hospital) Out-of-Hospital	**26.3%** [19.6%, 33.8%] (42) **12.5%** [7.8%, 18.6%] (20) **13.8%** [8.8%, 20.1%] (22)	**12.6%** [8.9%, 17.1%] (34) **7.0%** [4.3%, 10.8%] (19) **5.5%** [3.1%, 9.0%] (15)
Non-Q-Wave MI Total Early (In-Hospital) Out-of-Hospital	**10.6%** [6.3%, 16.5%] (17) **6.9%** [3.5%, 12.0%] (11) **3.8%** [1.4%, 8.0%] (6)	**1.1%** [0.2%, 3.2%] (3) **0.7%** [0.1%, 2.6%] (2) **0.4%** [0.0%, 2.0%] (1)
Q-Wave MI Early (In-Hospital) Out-of-Hospital	**0.6%** [0.0%, 3.4%] (1) **0.0%** [0.0%, 2.3%] (0) **0.6%** [0.0%, 3.4%] (1)	**1.1%** [0.2%, 3.2%] (3) **0.7%** [0.1%, 2.6%] (2) **0.4%** [0.0%, 2.0%] (1)
CABG Total Early (In-Hospital) Out-of-Hospital	**3.8%** [1.4%, 8.0%] (6) **0.6%** [0.0%, 3.4%] (1) **2.5%** [0.7%, 6.3%] (4)	**1.1%** [0.2%, 3.2%] (3) **0.0%** [0.0%, 1.4%] (0) **1.1%** [0.2%, 3.2%] (3)
Stent Thrombosis Total Early (In-Hospital) Out-of-Hospital	**0.0%** [0.0%, 2.3%] (0) **0.0%** [0.0%, 2.3%] (0) **0.0%** [0.0%, 2.3%] (0)	**1.1%** [0.2%, 3.2%] (3) **0.7%** [0.1%, 2.6%](2) **0.4%** [0.0%, 2.0%] (1)
Death Total Early (In-Hospital) Out-of-Hospital	**3.1%** [1.0%, 7.1%] (5) **0.6%** [0.0%, 3.4%] (1) **2.5%** [0.7%, 6.3%] (4)	**0.4%** [0.0%, 2.0%] (1) **0.4%** [0.0%, 2.0%] (1) **0.0%** [0.0%, 1.4%] (0)
Bleeding Complications Vascular Complications Cerebrovascular Accident	**3.8%** [1.4%, 8.0%] (6) **3.1%** [1.0%, 7.1%] (5) **1.9%** [0.4%, 5.4%] (3)	**2.6%** [1.0%, 5.3%] (7) **4.8%** [2.6%, 8.1%] (13) **0.4%** [0.0%, 2.0%] (1)
Stent Delivery Failure	**2.8%** [0.9%, 6.4%] (5)*	**0.0%** [0.0%, 1.4%] (0)

- The 95% confidence interval for one proportion was calculated using Exact Clopper-Pearson CI.
- Any Adverse event includes death, Q-Wave MI, Non-Q-Wave MI, emergent CABG, target lesion revascularization, stent thrombosis, bleeding complications, vascular complications, and CVA.
- Early (In-Hospital) refers to events during the hospitalization for the initial stent placement.
- In cases where a patient experienced both an In-Hospital and an Out-of-Hospital event, they are counted once in each group, however, they are counted only once in the event total. Hence, the sum of the In-hospital event rate and the Out-of-Hospital event rate may not equal the total event rate.
- See Table 6 Footnotes for additional REVIVE Study definitions.

***** Per protocol, as many as two lesions per target vessel could be treated. Device success by QCA is calculated per lesion (n = 179).

6.1.3 CADILLAC Trial – Acute Myocardial Infarction

Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications

Guidant MULTI-LINK and Guidant MULTI-LINK DUET Coronary Stent System
Based on equivalency in *de novo* lesions and the similarities in design and manufacture of the Guidant MULTI-LINK DUET Coronary Stent Systems, the following study data demonstrates suitability of the Guidant MULTI-LINK VISION Coronary Stent System for use in acute myocardial infarctions as defined below.

The CADILLAC Trial was a prospective, randomized study to determine the comparative MACE rates (defined as the composite of death, disabling stroke, reinfarction and ischemia-driven revascularization by CABG or PTCA related to the target vessel), subacute thrombosis (SAT) and bleeding events. The study was conducted at 74 sites including the United States, Europe and South America. After satisfying clinical and angiographic criteria, 2,082 patients were randomized equally to one of four reperfusion strategies, which were PTCA alone, PTCA plus abciximab, stent alone or stent plus abciximab.

Patients with clinical symptoms of acute MI (without cardiogenic shock) of at least 30 minutes in duration but no more than 12 hours were screened for eligibility. Angiographic confirmation was required to assure that the lesion was in a native coronary lesion, not previously stented, and visually estimated to be between 2.5 mm and 4.0 mm in diameter. Lesions had to be covered by no more than two stents, each of which was $\leq$ 38 mm in length.

Table 4 summarizes the Principal Adverse Events of the CADILLAC Trial at 180 days.

Table 4: CADILLAC Trial – Principal Adverse Events through 180 Days

% [95% confidence interval] (number / denominator)

	PTCA (n = 518)	PTCA plus Abciximab (n = 528)	Stent (n = 512)	Stent plus Abciximab (n = 524)
Any Adverse Event	**26.4%** [22.7%, 30.5%] (137)	**22.3%** [18.9%, 26.1%] (118)	**18.6%** [15.3%, 22.2%] (95)	**14.9%** [11.9%, 18.2%] (78)
Early (In-Hospital)	**10.4%** [7.9%, 13.4%] (54)	**5.7%** [3.9%, 8.0%] (30)	**10.2%** [7.7%, 13.1%] (52)	**5.5%** [3.7%, 7.9%] (29)
Out-of-Hospital	**16.0%** [13.0%, 19.5%] (83)	**16.7%** [13.6%, 20.1%] (88)	**8.4%** [6.1%, 11.1%] (43)	**9.4%** [7.0%, 12.2%] (49)
Any MACE	**19.7%** [16.4%, 23.4%] (102)	**16.3%** [13.2%, 19.7%] (86)	**11.3%** [8.7%, 14.4%] (58)	**10.1%** [7.7%, 13.0%] (53)
Early (In-Hospital)	**6.0%** [4.1%, 8.4%] (31)	**2.7%** [1.5%, 4.4%] (14)	**4.9%** [3.2%, 7.1%] (25)	**2.9%** [1.6%, 4.7%] (15)
Out-of-Hospital	**13.7%** [10.9%, 17.0%] (71)	**13.6%** [10.8%, 16.9%] (72)	**6.4%** [4.5%, 8.9%] (33)	**7.3%** [5.2%, 9.8%] (38)
MI	**1.7%** [0.8%, 3.3%] (9)	**2.7%** [1.5%, 4.4%] (14)	**1.6%** [0.7%, 3.1%] (8)	**2.1%** [1.1%, 3.7%] (11)
Early (In-Hospital)	**0.2%** [0.0%, 1.1%] (1)	**0.0%** [0.0%, 0.7%] (0)	**0.8%** [0.2%, 2.0%] (4)	**0.0%** [0.0%, 0.7%] (0)
Out-of-Hospital	**1.5%** [0.7%, 3.0%] (8)	**2.7%** [1.5%, 4.4%] (14)	**0.8%** [0.2%, 2.0%] (4)	**2.1%** [1.1%, 3.7%] (11)
Ischemic TVR–CABG	**3.1%** [1.8%, 5.0%] (16)	**3.0%** [1.7%, 4.9%] (16)	**2.7%** [1.5%, 4.5%] (14)	**1.5%** [0.7%, 3.0%] (8)
Early (In-Hospital)	**1.5%** [0.7%, 3.0%] (8)	**0.6%** [0.1%, 1.7%] (3)	**1.2%** [0.4%, 2.5%] (6)	**0.6%** [0.1%, 1.7%] (3)
Out-of-Hospital	**1.5%** [0.7%, 3.0%] (8)	**2.5%** [1.3%, 4.2%] (13)	**1.6%** [0.7%, 3.1%] (8)	**1.0%** [0.3%, 2.2%] (5)
Ischemic TVR-PTCA	**12.0%** [9.3%, 15.1%] (62)	**10.6%** [8.1%, 13.6%] (56)	**5.5%** [3.7%, 7.8%] (28)	**3.4%** [2.0%, 5.4%] (18)
Early (In-Hospital)	**2.9%** [1.6%, 4.7%] (15)	**0.9%** [0.3%, 2.2%] (5)	**1.8%** [0.8%, 3.3%] (9)	**0.4%** [0.0%, 1.4%] (2)
Out-of-Hospital	**9.1%** [6.7%, 11.9%] (47)	**9.7%** [7.3%, 12.5%] (51)	**3.7%** [2.2%, 5.7%] (19)	**3.1%** [1.8%, 4.9%] (16)
Subacute Thrombosis *	**1.9%** [0.9%, 3.5%] (10)	**0.8%** [0.2%, 1.9%] (4)	**1.0%** [0.3%, 2.3%] (5)	**0.0%** [0.0%, 0.7%] (0)
Early (In-Hospital)	**1.4%** [0.5%, 2.8%] (7)	**0.4%** [0.0%, 1.4%] (2)	**1.0%** [0.3%, 2.3%] (5)	**0.0%** [0.0%, 0.7%] (0)
Out-of-Hospital	**0.6%** [0.1%, 1.7%] (3)	**0.4%** [0.0%, 1.4%] (2)	**0.0%** [0.0%, 0.7%] (0)	**0.0%** [0.0%, 0.7%] (0)
Death	**4.4%** [2.8%, 6.6%] (23)	**2.5%** [1.3%, 4.2%] (13)	**2.9%** [1.6%, 4.8%] (15)	**4.2%** [2.6%, 6.3%] (22)
Early (In-Hospital)	**1.5%** [0.7%, 3.0%] (8)	**1.1%** [0.4%, 2.5%] (6)	**2.0%** [0.9%, 3.6%] (10)	**1.9%** [0.9%, 3.5%] (10)
Out-of-Hospital	**2.9%** [1.6%, 4.7%] (15)	**1.3%** [0.5%, 2.7%] (7)	**1.0%** [0.3%, 2.3%] (5)	**2.3%** [1.2%, 4.0%] (12)
Bleeding Complications *	**3.1%** [1.8%, 5.0%] (16)	**2.7%** [1.5%, 4.4%] (14)	**4.5%** [2.9%, 6.7%] (23)	**3.2%** [1.9%, 5.1%] (17)
Early (In-Hospital)	**2.9%** [1.6%, 4.7%] (15)	**2.7%** [1.5%, 4.4%] (14)	**3.3%** [1.9%, 5.3%] (17)	**2.7%** [1.5%, 4.4%] (14)
Out-of-Hospital	**0.2%** [0.0%, 1.1%] (1)	**0.0%** [0.0%, 0.7%] (0)	**1.2%** [0.4%, 2.5%] (6)	**0.6%** [0.1%, 1.7%] (3)
Disabling Stroke (CVA)	**0.2%** [0.0%, 1.1%] (1)	**0.2%** [0.0%, 1.1%] (1)	**0.4%** [0.0%, 1.4%] (2)	**0.4%** [0.0%, 1.4%] (2)
Early (In-Hospital)	**0.0%** [0.0%, 0.7%] (0)	**0.0%** [0.0%, 0.7%] (0)	**0.2%** [0.0%, 1.1%] (1)	**0.0%** [0.0%, 0.7%] (0)
Out-of-Hospital	**0.2%** [0.0%, 1.1%] (1)	**0.2%** [0.0%, 1.1%] (1)	**0.2%** [0.0%, 1.1%] (1)	**0.4%** [0.0%, 1.4%] (2)

- Displayed are 95% exact Clopper-Pearson confidence intervals for one proportion.
- Any Adverse Event counts are straight sums across the individual events. All other counts are patient counts, with patients counted only once at each level of summation.
- Any Adverse Event includes MI (Myocardial Infarction), ischemic TVR (Target Vessel Revascularization) – CABG (Coronary Artery Bypass Graft surgery) and PTCA (Percutaneous Transluminal Coronary Angioplasty), subacute thrombosis, death, bleeding complication, and CVA (Cerebrovascular Accident / Disabling stroke).
- CABG and PTCA are ischemic events at the target vessel, as defined in the study protocol.
- Disabling stroke (CVA) is protocol-defined as an acute, new neurological deficit lasting > 24 hours affecting daily activities, or resulting in death.
- Note that only the first occurrence of each event for each patient was recorded in the adjudicated dataset. As a result, only the first of each event is counted for each patient.
- See Table 7 Footnotes for additional CADILLAC Trial definitions.

* Counts for subacute thrombosis and bleeding complications are through 30 days.

6.2 Potential Adverse Events

Adverse events may be associated with the use of a coronary stent in native coronary arteries:

- Acute myocardial infarction
- Arrhythmias, including VF and VT
- Death
- Dissection
- Drug reactions to antiplatelet agents / contrast medium
- Emboli, distal (air, tissue or thrombotic emboli)
- Emergent coronary artery bypass surgery
- Hemorrhage, requiring transfusion
- Hypotension / hypertension
- Infection and / or pain at insertion site
- Ischemia, myocardial
- Perforation
- Pseudoaneurysm, femoral
- Restenosis of stented segment
- Spasm
- Stent embolization
- Stent thrombosis / occlusion
- Stroke / cerebrovascular accident
- Total occlusion of coronary artery

7.0 CLINICAL STUDIES

7.1 VISION Registry – *de novo* Lesions

Purpose: To assess the safety and efficacy of the Guidant MULTI-LINK VISION RX Coronary Stent System in reducing target vessel failure in *de novo* native coronary artery lesions.

Conclusions: In selected patients, the VISION Registry demonstrated the 180-day and 270-day safety and efficacy of this stent for the treatment of patients with *de novo* lesions in native coronary arteries.

Design: A prospective, non-randomized, multi-center, global (18 North American, 1 European and 3 Asia-Pacific sites), consecutive enrollment study. Patients were at least 18 years of age, with angina or a positive functional study, undergoing elective, single *de novo* lesion treatment in a native coronary artery. Patients were required to have a target vessel with the following coronary angiographic features: major coronary artery or major branch with a visually estimated stenosis of $\geq$ 50% and $<$ 100%, a reference diameter visually estimated to be $\geq$ 3.0 mm and $\leq$ 4.0 mm, and a lesion length visually estimated to be $\leq$ 25 mm.

The primary endpoint for the VISION Registry was target vessel failure (TVF) at 180 days, defined as a composite of death, Q-Wave MI, non-Q-Wave MI, TSR, or TVR by CABG or PCI. The primary endpoint was analyzed on an intent-to-treat basis defined as patients who had the investigational device introduced into the body (stent system advanced through distal end of the guiding catheter). Secondary endpoints, including but not limited to angiographic in-stent binary restenosis, TVF and MACE at 270 days, were analyzed on a per-protocol evaluable basis defined as patients who had successful procedures and were available for follow-up.

All patients received the hospital's standard anticoagulant and antiplatelet regimen for coronary stent implantation. The ACT was monitored and recorded on source documentation during the procedure. The ACT was kept at a therapeutic level for percutaneous coronary interventions per the hospital standard.

Demography: The total population consisted of 268 patients, but analysis was performed on 267 patients because one patient had the Guidant MULTI-LINK VISION Coronary Stent implanted in an SVG. Baseline characteristics for the VISION Registry indicated 68.2% were male and ranged in age from 37 to 91 years with an average age of 63.6 ±10.7 (mean ±SD), 23.2% had diabetes requiring medication, 61.4% had hypertension requiring medication, 23.6% were current smokers, and 63.7% had hyperlipidemia requiring medication. From a clinical perspective, the patient demographics were similar between the VISION and TETRA Registries.

Methods: Clinical or telephone follow-up was collected In-Hospital and at 14, 30, 180, 270 and 365 days. 80.9% (216/267) of VISION Registry patients underwent angiographic follow-up at the 180-day clinical visit. Guidant personnel performed data monitoring. The angiographic core lab adjudicated revascularizations by PCI. An independent Clinical Events Committee adjudicated all other primary endpoints.

Results: In the VISION Registry, the 180-day and 270-day TVF rates were 6.7% and 14.7% (respectively); in the TETRA Registry, the 180-day TVF rate was 12.8%. The representative sample of patients from the VISION Registry followed clinically for up to 9 months (270 days) demonstrates that the clinical outcomes achieved with the MULTI-LINK VISION CSS are similar to those observed at 180 days in the TETRA Registry. No unanticipated events that might affect the risk analysis were noted in the VISION Registry. Adverse event rates are presented in Table 2.

Table 5 compares the principal effectiveness and safety results of patients treated in the VISION Registry at 180 and 270 days to those treated in the TETRA Registry at 180 days.

Table 5: VISION Registry – Principal Effectiveness and Safety Results through 180 and 270 Days

% [95% confidence interval] (number / denominator), or mean ±SD {range} (number)

	MULTI-LINK VISION Stent – 180 Days (n = 267) [1]	MULTI-LINK TETRA Stent – 180 Days (n = 202)	MULTI-LINK VISION Stent – 270 Days (n = 267) [1]
Effectiveness Measures			
Device Success by QCA	100% [98.6%, 100.0%] (267 / 267)	99.5% [97.3%, 100.0%] (201 / 202)	100% [98.6%, 100.0%] (267 / 267)
Procedure Success by QCA	98.9% [96.8%, 99.8%] (264 / 267)	97.5% [94.3%, 99.2%] (197 / 202)	98.9% [96.8%, 99.8%] (264 / 267)
Binary Restenosis Rate	15.7% [11.2%, 21.3%] (34 / 216)	23.6% [17.5%, 30.6%] (41 / 174)	N/A
Post-Procedure In-Stent %DS	4.9% ± 9.2% (266) {-20.1%, 31.9%} [3.8%, 6.0%]	5.7% ± 8.4% (201) {-43.1%, 28.9%} [4.6%, 6.9%]	N/A
Follow-up In-Stent %DS	29.2% ± 19.2% (216) {-7.4%, 100%} [26.6%, 31.8%]	34.6% ± 22.7% (173) {-9.2%, 98.0%} [31.2%, 38.0%]	N/A
Safety Measures			
In-Hospital MACE Rate	1.5% [0.4%, 3.8%] (4 / 267)	2.0% [0.5%, 5.0%] (4 / 202)	1.5% [0.4%, 3.8%] (4 / 267)
Out-of-hospital MACE Rate	5.0% [2.7%, 8.5%] (13 / 258)	10.2% [6.3%, 15.3%] (20 / 196)	11.6% [8.0%, 16.1%] (30 / 259)
MACE Rate	6.2% [3.6%, 9.9%] (16 / 258)	12.2% [8.0%, 17.7%] (24 / 196)	12.7% [8.9%, 17.4%] (33 / 259)
TVF Rate	6.7% [4.0%, 10.4%] (18 / 267)	12.8% [8.4%, 18.3%] (25 / 196)	14.7% [10.6%, 19.6%] (38 / 259)
Survival	98.8% [96.6%, 99.8%] (255 / 258)	99.5% [97.2%, 100.0%] (195 / 196)	98.8% [96.7%, 99.8%] (256 / 259)
TVF Free (KM)	92.9%	86.4%	85.5%
Target Site Revascularization Free (KM)	94.8%	88.5%	88.4%
Target Vessel Revascularization (not at Target Site) Free (KM)	98.4%	N/A	97.3%
Subacute Thrombosis *	0.4% [0.0%, 2.1%] (1 / 258)	0% [0.0%, 1.9%] (0 / 196)	0.4% [0.0%, 2.1%] (1 / 259)
Bleeding Complications	2.3% [0.9%, 5.0%] (6 / 258)	3.1% [1.1%, 6.5%] (6 / 196)	2.7% [1.1%, 5.5%] (7 / 259)
Vascular Complications	1.6% [0.4%, 3.9%] (4 / 258)	4.6% [2.1%, 8.5%] (9 / 196)	1.9% [0.6%, 4.4%] (5 / 259)
Hospitalization Post-Intervention (days)	1.3 ± 1.0 {0, 10} [1.2, 1.4] (267)	1.3 ± 0.8 {0, 6} [1.2, 1.4] (201)	1.3 ± 1.0 {0, 10} [1.2, 1.4] (267)

[1] 268 patients enrolled but one patient is excluded because the MULTI-LINK VISION stent was implanted in an SVG, so n = 267.
Primary endpoint (180-day TVF) was analyzed on an intent-to-treat basis, n = 267.
180-day clinical data was available on 258 patients for the VISION Registry and 196 patients for the TETRA Registry.
180-day angiographic data was available on 216 patients for the VISION Registry and 174 patients for the TETRA Registry.
Secondary endpoints were analyzed on per protocol evaluable patients. There were n = 258 patients available at the 180 day f/u time point and there were n = 259 patients available at the 270 day f/u time point.
KM = Kaplan-Meier.
* Subacute Thrombosis is based on 30 days.

VISION Registry Definitions

- **QCA** – Quantitative Coronary Angiography.
- **Device Success** – Attainment of final result of < 50% residual stenosis of the target site using the designated treatment device.
- **Procedure Success** – Attainment of final result of < 50% residual stenosis of the target site using the designated treatment device and any other adjunctive device, including additional stents, without death, emergent bypass surgery, or Q-Wave or Non-Q-Wave MI post procedure prior to hospital discharge.
- **Binary restenosis** – ≥ 50% by QCA.
- **% DS** – Percent diameter stenosis by QCA.
- **In-Hospital MACE** – Any MACE occurring prior to hospital discharge.
- **Out-of-Hospital MACE** – Any MACE occurring from hospital discharge through 180-day clinical follow-up.
- **Major Adverse Cardiac Event (MACE)** – The composite of death, Q-Wave MI, Non-Q-Wave MI and Target Site Revascularization (TSR) by Coronary Artery Bypass Surgery (CABG) or Percutaneous Coronary Intervention (PCI).
- **Target Vessel Failure (TVF)** – The composite of death, Q-Wave MI, Non-Q-Wave MI, Target Site Revascularization (TSR) or Target Vessel Revascularization (TVR) by Coronary Artery Bypass Graft Surgery (CABG) or Percutaneous Coronary Intervention (PCI).
- **Target Site Revascularization (TSR)** – Repeat Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG) surgery.
- **Subacute Thrombosis (SAT)** – Any cardiac death < 30 days. Any subacute (outside of cath lab) closure requiring revascularization of the target site < 30 days with presence of thrombus at the target site, any total closure indicated by Quantitative Coronary Angiography (QCA) < 30 days.
- **Bleeding Complication** – Blood loss necessitating a transfusion.
- **Vascular Complication** – Any hematoma > 5 cm, arteriovenous fistula, pseudoaneurysm, retroperitoneal bleed, peripheral nerve disorder or surgical repair.
- **Q-Wave Myocardial Infarction (QMI)** – The development of new abnormal Q-Waves not present on the patient's baseline ECG – through blinded evaluation by the ECG Core Laboratory – in association with CK enzyme elevation of three times upper normal limit and presence of CK-MB.
- **Non Q-Wave Myocardial Infraction (Non QMI)** – CK enzyme elevations by more than three times the upper limit of normal and presence of CK-MB.
- **CABG** – Coronary Artery Bypass Graft surgery.
- **PCI** – Percutaneous Coronary Intervention.
- **Cerebrovascular Accident (CVA)** – Acute, new neurologic deficit lasting > 24 hours affecting daily activities, or resulting in death, classified by a physician as a stroke.
- **Stent Delivery Failure** – Inability to deliver the stent to the intended target lesion.

7.2 REVIVE Study – Saphenous Vein Bypass Grafts

Guidant MULTI-LINK DUET RX Coronary Stent System

Based on equivalency in *de novo* lesions and the similarities in design and manufacture of the Guidant MULTI-LINK DUET Coronary Stent Systems, the following study data demonstrates suitability of the Guidant MULTI-LINK VISION Coronary Stent System for use in saphenous vein bypass grafts.

Purpose: To establish the safety and efficacy of stenting in saphenous vein bypass grafts (SVG).

Conclusions: The primary endpoint of Target Vessel Failure (TVF) rate at six months post-procedure for the 162 intent-to-treat patients was 19.8%, which is similar to the TVF rate of 20.0% for the 160 evaluable patients only. The upper CL of the TVF rate (25.6%) is less than 33%, therefore the alternative hypothesis would be accepted based on intent-to-treat patients.

Design: A prospective, non-randomized, multi-center, consecutive enrollment registry was conducted in 22 US centers. The primary endpoint of TVF at six months post-index procedure was defined as the composite of death, Q-Wave MI, non-Q-Wave MI and revascularization by CABG or PTCA attributable to the target vessel.

All patients presented with angina or a positive functional study and had up to two treatable target lesions in the target graft. The target vessel reference diameter requirement was visual estimation of the vessel to be $\geq$ 3.0 mm and $\leq$ 4.0 mm in diameter and $\leq$ 35 mm in length. Patients were allowed to have an intervention to one of the other two major epicardial vessels with an FDA approved device or another bypass graft.

All patients received the hospital's standard anticoagulant and antiplatelet regimen for coronary stent implantation. The ACT was monitored and recorded on source documentation during the procedure. The ACT was kept at a therapeutic level for percutaneous coronary interventions per the hospital standard.

Demography: The total population consisted of 162 patients, 160 of whom were evaluable; 82.5% were male ranging in age from 41 to 88 years with an average of 67.7 ±9.3 (mean ±SD). Current cigarette use, diabetes, hypertension and hyperlipidemia requiring medication were 11.9%, 25.6%, 58.8% and 67.5% respectively.

Methods: Using a specific monitoring regimen, data were collected at the index procedure, 2 weeks, 1 month and 6 months post-index procedure. A Clinical Events Committee (CEC) adjudicated all TVF and major adverse cardiac event (MACE) endpoints.

Results: The device success and procedure success rates for the Guidant MULTI-LINK DUET RX Coronary Stent System were 97.2% and 89.2%, respectively. No unanticipated events that might affect the risk analysis were noted in the REVIVE Study. Adverse event rates are presented in Table 3.

Table 6 summarizes the principal effectiveness and safety results of patients treated in the REVIVE Study.

Table 6: REVIVE Study – Principal Effectiveness and Safety Results through 180 Days

% [95% confidence interval] (number / denominator), or mean ± SD {range} (number)

	Guidant MULTI-LINK DUET SVG (n = 160)	**Guidant MULTI-LINK DUET *de novo* (n = 270)**
Effectiveness Measures		
Device Success by QCA *	**97.2%** [93.6%, 99.1%] (174 / 179)	**100%** [98.6%, 100%] (269 / 269)
Clinical Procedure Success by QCA	**89.2%** [83.3%, 93.6%] (141 / 158)	**98.1%** [95.7%, 99.4%] (264 / 269)
In-Stent % DS post procedure, mm	**9.2%** ± 8.8% {-16%, 41%}(174)	**9.7%** ± 9.9% {-31.9%, 34.3%} (269)
Target Lesion Revascularization (TLR)	**10.0%** [5.8%, 15.7%] (16 / 160)	**8.1%** [5.2%, 12.1%] (22 / 270)
Target Vessel Failure (TVF)	**20.0%** [14.1%, 27.0%] (32 / 160)	**9.6%** [6.4%, 13.8%] (26 / 270)
Safety Measures		
In-Hospital Clinical Event (MACE)	**8.1%** [4.4%, 13.5%] (13 / 160)	**1.9%** [0.6%, 4.3%] (5 / 270)
Out-of Hospital Clinical Event (MACE)	**11.9%** [7.3%, 17.9%] (19 / 160)	**8.5%** [5.5%, 12.5%] (23 / 270)
Bleeding Complication Rate	**3.8%** [1.4%, 8.0%] (6 / 160)	**2.6%** [1.0%, 5.3%] (7 / 270)
Vascular Event Rate	**3.1%** [1.0%, 7.1%] (5 / 160)	**4.8%** [2.6%, 8.1%] (13 / 270)
Subacute Thrombosis	**0.0%** [0.0%, 2.3%] (0 / 160)	**1.1%** [0.2%, 3.2%] (3 / 270)
MACE Rate at 180 days	**19.4%** [13.6%, 26.4%] (31 / 160)	**10.4%** [7.0%, 14.6%] (28 / 270)

*Per protocol, as many as two lesions per target vessel could be treated. Device Success by QCA is calculated per lesion (n = 179).

REVIVE Study Definitions

- **Device Success** – Attainment of final result < 50% (in-lesion) residual stenosis of the target site using Guidant MULTI-LINK Stent System alone (i.e., without the use of other types of stents or non-balloon devices).
- **Clinical Procedure Success** – < 50% diameter stenosis using Guidant MULTI-LINK Stent System and no In-Hospital MACE (death, Q-Wave MI, Non-Q-Wave MI, emergent CABG, or repeat target lesion revascularization).
- **QCA** – Quantitative Coronary Angiography.
- **% DS** – Percent diameter stenosis by QCA.
- **Target Lesion Revascularization (TLR)** – Repeat PTCA or CABG to the original site of intervention.
- **Target Vessel Failure (TVF)** – The composite of acute and late-term major events of death, Q-Wave MI or Non-Q-Wave MI, CABG, and percutaneous transluminal coronary angioplasty (PTCA) attributable to the target vessel.
- **MACE** – Major Adverse Cardiac Event: death, Q-Wave MI or Non-Q-Wave MI, CABG, or PTCA to the treated site.
- **In-Hospital Clinical Event** – Any MACE occurring prior to hospital discharge.
- **Out-of-Hospital Clinical Event** – Any MACE occurring from hospital discharge through 180-day clinical follow-up.
- **Bleeding Complication** – Blood loss necessitating a transfusion.
- **Vascular Complication** – Any hematoma > 5 cm, arteriovenous fistula, pseudoaneurysm, retroperitoneal bleed, peripheral nerve disorder or surgical repair.
- **Non-Q-Wave MI** – Non Q-Wave Myocardial Infarction**,** CK enzyme elevations by more than three times the upper limit of normal and presence of CK-MB.
- **Q-Wave MI** – Q-Wave Myocardial Infarction (The development of new abnormal Q-Waves not present on the patient's baseline ECG – through blinded evaluation by the ECG Core Laboratory – in association with CK enzyme elevation of three times upper normal limit and presence of CK-MB).
- **CABG** – Coronary Artery Bypass Graph surgery.
- **Stent Thrombosis** – Angiographic thrombus or subacute closure within the stented vessel, or any death not attributed to a non-cardiac cause in the absence of documented angiographic stent patency within the first 30 days.
- **Cerebrovascular Accident / CVA** – Acute, new neurologic deficit lasting > 24 hours affecting daily activities, or resulting in death, classified by a physician as a stroke.
- **Stent Delivery Failure** – Inability to deliver the stent to the intended target lesion.

7.3 CADILLAC Trial – Acute Myocardial Infarction

Guidant MULTI-LINK and Guidant MULTI-LINK DUET Coronary Stent System
Based on equivalency in *de novo* lesions and the similarities in design and manufacture of the Guidant MULTI-LINK DUET Coronary Stent Systems, the following study data demonstrates suitability of the Guidant MULTI-LINK VISION Coronary Stent System for use in acute myocardial infarctions as defined below.

Purpose: To compare the composite major adverse cardiac event (MACE) rates between reperfusion strategies as defined by four treatment arms: PTCA alone; PTCA plus abciximab; stent alone; stent plus abciximab.

Conclusions: In a comparison between PTCA and the Guidant coronary stent in selected patients presenting with acute myocardial infarction (MI), the stent provided similar immediate clinical benefits and resulted in reduced MACE rates at 180 days.

Design: A multi-center, prospective, randomized four-arm trial was conducted at 74 international sites: 61 United States, 7 European, and 6 South America. Patients with clinical symptoms of acute MI (without cardiogenic shock) of at least 30 minutes in duration but no more than 12 hours were screened for eligibility. Diagnosis of acute MI required ST segment elevation or angiographic evidence of high-grade stenosis with wall motion abnormality. Patients who satisfied clinical eligibility criteria were enrolled if the lesion was in a native coronary artery that was not previously stented, and that was visually estimated to be between 2.5 mm and 4.0 mm in diameter. Lesions had to be covered by no more than two stents, each of which was ≤ 38 mm in length.

Using a primary endpoint of 180 days, the MACE elements included death, disabling stroke, reinfarction, and ischemic Target Vessel Revascularization (TVR). Subacute Thrombosis (SAT) and bleeding complications were also compared.

Demography: The total population consisted of 2,082 patients: 518 PTCA alone; 528 PTCA plus abciximab; 512 stent alone; 524 stent plus abciximab. Baseline characteristics were similar across all four treatment arms; factors evaluated included age (median 59.0 years); height (68”); weight (180 lbs); diabetes (17%); pre-existing hypertension (48%); hyperlipidemia (38%); history of smoking (69%), and gender (27% females).

Methods: Using a specific monitoring regimen, data were collected at the index procedure, 2 weeks, 30 days, 6 months, 7 months (with a planned angiographic follow-up for a subset of patients), and 12 months. The data were submitted to a data management group for review and identification of discrepancies. The angiographic core lab determined angiographic outcomes. A clinical events committee performed concurrent reviews and adjudicated all MACE.

Results: The stent alone as compared to PTCA alone, and as compared to PTCA plus abciximab, proved to be statistically significant in reducing 180-day MACE rates, (11.3% vs. 19.7% $p < 0.001$, 11.3% vs. 16.3%, $p < 0.001$). The survival rates between all four reperfusion strategies were statistically similar: stent alone (97.1%), stent plus abciximab (95.8%), PTCA alone (95.6%) and PTCA plus abciximab (97.5%) at 180 days. No unanticipated events that might affect the risk analysis were noted in the CADILLAC Trial. Adverse event rates are presented in Table 4.

Table 7 summarizes the principal effectiveness and safety results of patients treated in the CADILLAC Trial at 180 days. Figure 1 provides the cumulative MACE rates to 365 days.

Table 7: CADILLAC Trial – Principal Effectiveness and Safety Results through 180 Days

Primary Endpoint First Comparison by Evaluating MACE
The first comparison was one of superiority between stent alone and PTCA alone. The stent alone arm of the trial proved to be significantly superior to PTCA alone (11.3% vs. 19.7, $p < 0.001$).

Primary Endpoint Second Comparison by Evaluating MACE
The second comparison was a test of equivalency between stent alone and PTCA plus abciximab. The stent alone arm of the trial proved to be not only equivalent, but significantly superior to PTCA plus abciximab (11.3% vs. 16.3%, $p < 0.001$).

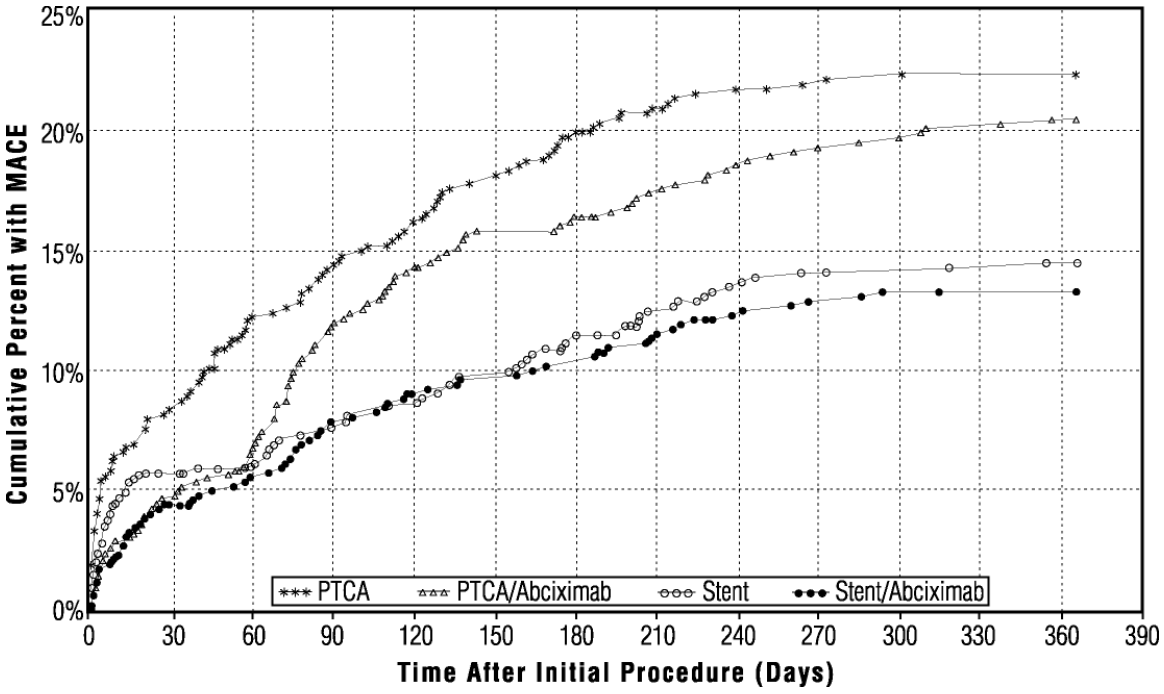
	PTCA Alone (n = 518)	PTCA plus Abciximab (n = 528)	Stent Alone (n = 512)	Stent plus Abciximab (n = 524)
Efficacy Measures				
Lesion Success by QCA	**93.1%** (461 / 495)	**94.2%** (483 / 513)	**94.2%** (457 / 485)	**96.8%** (491 / 507)
Clinical Procedure Success by QCA	**88.1%** (436 / 495)	**92.0%** (472 / 513)	**90.7%** (440 / 485)	**95.1%** (482 / 507)
Post Procedure MLD (mm), in-lesion / in-stent Mean ±SD (N) Range (min-max)	**2.24 ± 0.50** (501) (0.40, 3.95)	**2.21 ± 0.55** (516) (0.00, 4.86)	**2.63 ± 0.48** (487) (0.00, 4.18)	**2.71 ± 0.48** (507) (0.00, 4.41)
7-Month Follow up in-lesion / in-stent % DS Angiographic Subset Patients Mean ±SD (N)	**45.10 ± 25.15** (144) (-4.70,100.0)	**48.60 ± 23.55** (163) (3.30, 100.0)	**30.81 ± 18.87** (138) (-21.3, 100.0)	**32.44 ± 19.63** (162) (-28.5, 100.0)
7-Month Follow up in-lesion / in-stent binary restenosis rate Angiographic Subset Patients	**34.7%** (50 / 144)	**44.8%** (73 / 163)	**13.8%** (19 / 138)	**17.9%** (29 / 162)
TVR-free through 6 months	**83.8%** (434 / 518)	**85.6%** (452 / 528)	**91.4%** (468 / 512)	**94.5%** (495 / 524)
TVF-free through 6 months	**79.3%** (411 / 518)	**83.0%** (438 / 528)	**88.3%** (452 / 512)	**89.5%** (469 / 524)
Safety Measures				
In-Hospital MACE Events	**6.0%** (31 / 518)	**2.7%** (14 / 528)	**4.9%** (25 / 512)	**2.9%** (15 / 524)
Out-of-Hospital MACE Events Through 180 Days	**13.7%** (71 / 518)	**13.6%** (72 / 528)	**6.4%** (33 / 512)	**7.3%** (38 / 524)
Bleeding Complications **	**3.1%** (16 / 518)	**2.7%** (14 / 528)	**4.5%** (23 / 512)	**3.2%** (17 / 524)
Subacute thrombosis **	**1.9%** (10 / 518)	**0.8%** (4 / 528)	**1.0%** (5 / 512)	**0.0%** (0 / 524)
Survival through 30 Days	**97.5%** (505 / 518)	**98.9%** (522 / 528)	**97.9%** (501 / 512)	**97.3%** (510 / 524)
Survival through 180 Days	**95.6%** (495 / 518)	**97.5%** (515 / 528)	**97.1%** (497 / 512)	**95.8%** (502 / 524)
MACE rate through 180 Days *	**19.7%** (102 / 518)	**16.3%** (86 / 528)	**11.3%** (58 / 512)	**10.1%** (53 / 524)
Length of Hospitalization - US Sites (days) Mean ±SD (N) Range (min-max)	**4.26 ± 2.78** (418) (1.00, 28.00)	**3.74 ± 2.43** (424) (1.00, 25.00)	**4.33 ± 3.58** (409) (0.00, 39.00)	**3.80 ± 2.51** (423) (1.00,23.00)
Length of Hospitalization - European Sites (days) Mean ±SD (N) Range (min-max)	**8.10 ± 4.63** (72) (2.00, 22.00)	**8.03 ± 5.28** (74) (2.00, 24.00)	**8.01 ± 4.65** (73) (3.00, 20.00)	**8.52 ± 6.06** (71) (2.00, 27.00)

CADILLAC Trial Definitions

- **QCA** – Quantitative Coronary Angiography.
- **Lesion success** – Attainment of final result, < 50% residual stenosis of the target site with TIMI 3 flow, using Guidant MULTI-LINK System or PTCA and any adjunctive device.
- **Clinical Procedure success** – Lesion Success without death, emergency bypass surgery, repeat PTCA of the target vessel or re-infarction (QMI or non-QMI) within seven days of the procedure.
- **MLD** – Minimal Lumen Diameter.
- **% DS** – Percent diameter stenosis by QCA.
- **Binary restenosis** – ≥ 50% by quantitative coronary analysis.
- **Target Vessel Revascularization (TVR)** – Bypass surgery or repeat angioplasty precipitated by an ischemic event (angina or a positive exercise test) (each event will be adjudicated by the CEAC).
- **Target Vessel Failure (TVF)** – The composite of acute and late-term major events of death, Q-Wave MI or Non-Q-Wave MI, CABG, and Percutaneous Transluminal Coronary Angioplasty (PTCA) attributable to the target vessel.
- **In-Hospital MACE** – Any MACE occurring prior to hospital discharge.
- **Out-of-Hospital MACE** – Any MACE occurring from hospital discharge through 180-day clinical follow-up.
- **MACE** – death, repeat Myocardial Infarction (Q-Wave or Non-Q-Wave MI), ischemia-driven TVR including Coronary Artery Bypass surgery (CABG), Percutaneous Intervention (PTCA with or without stent) and non-fatal disabling stroke.
- **Bleeding Complications** – Blood loss necessitating a transfusion, may include a gastrointestinal (GI) bleed, and hemoglobin drop of > 5 g/dl) documented on the Hemorrhagic Event CRF.
- **Subacute Thrombosis (SAT)** – Any cardiac death < 30 days. Any subacute (outside of cath lab) closure requiring revascularization of the target site < 30 days with presence of thrombus at the target site, any total closure indicated by Quantitative Coronary Angiography (QCA) < 30 days.
- **Disabling Stroke / CVA** – Acute, new neurologic deficit lasting > 24 hours affecting daily activities, or resulting in death, classified by a physician as a stroke.

* Primary Endpoint
** Counts for subacute thrombosis and bleeding complications are through 30 days.

Figure 1 Kaplan – Meier Curve of Time to MACE (to 365 days)



Time after Initial Procedure (days)								
Treatment	**Parameter**	**0**	**14**	**30**	**90**	**180**	**270**	**365**
PTCA	# At Risk	518	505.5	478	467	431	398.5	386
	# Events	10	35	43	74	102	112	114
	% with Event	1.93	6.78	8.34	14.43	19.98	21.99	22.4
	% SEM	0.6	1.11	1.22	1.55	1.77	1.84	1.85
PTCA plus Abciximab	# At Risk	528	525	508.5	497	457	431	414
	# Events	2	16	25	63	86	101	107
	% with Event	0.38	3.04	4.75	12.03	16.46	19.37	20.54
	% SEM	0.27	0.75	0.93	1.42	1.62	1.73	1.77
Stent	# At Risk	512	504.5	479	474	461	438	421.5
	# Events	5	27	29	39	58	71	73
	% with Event	0.98	5.29	5.69	7.68	11.48	14.11	14.52
	% SEM	0.43	0.99	1.03	1.18	1.42	1.55	1.57
Stent plus Abciximab	# At Risk	524	523	505.5	496	475.5	461	444.5
	# Events	1	17	23	41	53	67	69
	% with Event	0.19	3.24	4.39	7.86	10.19	12.92	13.31
	% SEM	0.19	0.77	0.9	1.18	1.33	1.47	1.49
Tests Between Groups	Test	Chi-Square	Deg Frdm	P-value				
Stent vs. PTCA	Log-Rank	10.9987	1	0.0009				
Stent vs. PTCA plus Abciximab	Log-Rank	6.0671	1	0.0138				

8.0 PATIENT SELECTION AND TREATMENT

8.1 Individualization of Treatment

The risks and benefits described above should be considered for each patient before use of the MULTI-LINK VISION RX or MULTI-LINK VISION OTW Coronary Stent Systems. Patient selection factors to be assessed should include a judgment regarding risk of antiplatelet therapy.

In *de novo* lesions in native coronary arteries, premorbid conditions that increase the risk of binary in-stent restenosis (diabetes mellitus and tobacco use) should be reviewed. The relationship of baseline and procedural variables to binary in-stent restenosis was examined. The univariate predictors of angiographic in-stent binary restenosis with $p < 0.05$ included post procedure in-stent Minimal Lumen Diameter (MLD), post procedure Reference Vessel Diameter (RVD) and pre-procedure RVD. Lesion length was close with a p-value of 0.0954. The multivariate predictors of angiographic in-stent binary restenosis with $p < 0.05$ included post-procedure in-stent MLD.

Thrombosis following stent implantation is affected by several baseline angiographic and procedural factors. These include vessel diameter less than 3.0 mm, intra-procedural thrombus, or poor distal runoff, dissection following stent implantation, and / or cessation of antiplatelet therapy (ticlopidine / ASA) within 30 days of stent implantation. In patients who have undergone coronary stenting, the persistence of a thrombus or dissection should be considered a marker for subsequent thrombotic occlusion. These patients should be monitored very carefully during the first month after stent implantation.

8.2 Use in Specific Patient Populations

The safety and effectiveness of the MULTI-LINK VISION Coronary Stent have not been established in:

- Patients with **unresolved vessel thrombus** at the lesion site.
- Patients with coronary artery reference vessel diameter < 3.0 mm.
- Patients with lesions located in the left main coronary artery, ostial lesions or lesions located at a bifurcation.
- Patients with diffuse disease or **poor outflow distal** to the identified lesions.
- Patients with **more than two overlapping stents** due to risk of thrombosis and restenosis.

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters to treat in-stent stenosis have not been established.

9.0 CLINICIAN USE INFORMATION

9.1 Inspection Prior to Use

Prior to using the MULTI-LINK VISION RX or MULTI-LINK VISION OTW Coronary Stent System, carefully remove the system from the package and inspect for bends, kinks, and other damage. Verify that the stent does not extend beyond the radiopaque balloon markers. Do not use if any defects are noted.

9.2 Materials Required

- Appropriate guiding catheter(s)
- 2 – 3 syringes (10 to 20 cc)
- 1,000 u / 500 cc Heparinized Normal Saline (HepNS)
- 0.014 inch (maximum) x 175 cm (minimum length) guide wire
- Rotating hemostatic valve with 0.096 inch minimum inner diameter
- 60% contrast diluted 1:1 with normal saline
- Inflation device
- Three-way stopcock
- Torque device
- Guide wire introducer

9.3 Preparation

9.3.1 Guide Wire Lumen Flush

1. Remove the protective cover from the tip.
2. For use with the MULTI-LINK VISION RX Coronary Stent System, flush the guide wire lumen with HepNS until fluid exits **the guide wire exit notch**.

   For use with the MULTI-LINK VISION OTW Coronary Stent System, flush the guide wire lumen with HepNS until fluid exits **the distal tip**.

9.3.2 Delivery System Preparation

1. Prepare an inflation device / syringe with diluted contrast medium.
2. Attach an inflation device / syringe to stopcock; attach it to the inflation port.
3. With the tip down, orient the delivery system vertically.
4. Open the stopcock to the delivery system; pull negative for 30 seconds; release to neutral for contrast fill.
5. Close the stopcock to the delivery system; purge the inflation device / syringe of all air.
6. Repeat steps 3 through 5 until all air is expelled.

   Note: If air is seen in the shaft, repeat **Delivery System Preparation** steps 3 through 5 to prevent uneven stent expansion.
7. If a syringe was used, attach a prepared inflation device to the stopcock.
8. Open the stopcock to the delivery system.
9. Leave on neutral.

9.4 Delivery Procedure

1. Prepare vascular access site according to standard practice.
2. Pre-dilate the lesion with a PTCA catheter. (In saphenous vein bypass graft lesions, pre-dilatation may be performed at the discretion of the operator.)
3. Maintain neutral pressure on inflation device. Open rotating hemostatic valve as widely as possible.
4. Back load delivery system onto proximal portion of guide wire while maintaining guide wire position across target lesion.

5. Advance delivery system over guide wire to target lesion. Utilize radiopaque balloon markers to position stent across lesion; perform angiography to confirm stent position.

   Note: Should **any resistance** be felt **at any time** during either lesion access or removal of delivery system post-stent implantation, the entire system should be **removed as a single unit**. See **Stent / System Removal – Precautions** for specific delivery system removal instructions.

6. Tighten the rotating hemostatic valve. Stent is now ready to be deployed.

9.5 Deployment Procedure

1. **CAUTION: Refer to the product label and the compliance chart in 9.6 below for *in vitro* stent inner diameter, nominal pressure and RBP. Deploy stent slowly by pressurizing delivery system in 2 atm increments, every 5 seconds, until stent is completely expanded. Maintain pressure for 30 seconds. If necessary, the delivery system can be repressurized or further pressurized to assure complete apposition of the stent to the artery wall. Do not exceed RBP.**

   FURTHER EXPANSION OF THE DEPLOYED STENT:

   If the deployed stent size is still inadequate with respect to reference vessel diameter, a larger balloon may be used to further expand the stent. If the initial angiographic appearance is sub-optimal, the stent may be further expanded using a low profile, high pressure, non-compliant balloon dilatation catheter. If this is required, the stented segment should be carefully recrossed with a prolapsed guide wire to avoid disrupting the stent geometry. Deployed stents should not be left under-dilated.

   CAUTION: Do not dilate the stent beyond the following limits.

Nominal Stent Diameter	Dilatation Limit
3.0 mm	**3.75 mm**
3.5 to 4.0 mm	**4.5 mm**

2. Deflate balloon by pulling negative on inflation device for 30 seconds.

9.6 *In Vitro* Information

Table 8: Typical MULTI-LINK VISION Stent & Balloon Compliance

Stent Diameter (mm)	Inflation Pressure (atm)									
	9	10	11	12	13	14	15	16	17	18
3.00	2.96	3.03	3.09	3.14	3.18	3.23	3.26	3.30	3.34	3.38
3.50	3.51	3.59	3.66	3.72	3.77	3.82	3.86	3.91	3.95	3.99
4.00	3.96	4.04	4.11	4.17	4.22	4.27	4.32	4.36	4.41	4.45
	Nominal							RBP*		

***DO NOT EXCEED RBP.** The Compliance Data are based on *in vitro* bench testing at 37°C.

9.7 Removal Procedure

1. Ensure delivery system is fully deflated.
2. Fully open rotating hemostatic valve.
3. While maintaining guide wire position and negative pressure on inflation device, withdraw delivery system.

   Note: Should **any resistance** be felt **at any time** during either lesion access or removal of delivery system post-stent implantation, the entire system should be **removed as a single unit**. See **Stent / System Removal – Precautions** for specific delivery system removal instructions.
4. Tighten the rotating hemostatic valve.
5. Repeat angiography to assess stented area.

   If post dilatation is necessary, ensure final stent diameter matches reference vessel diameter. **ASSURE THAT THE STENT IS NOT UNDER-DILATED.**

10.0 PATIENT INFORMATION

In addition to this Instructions for Use booklet, the MULTI-LINK VISION RX and MULTI-LINK VISION OTW Coronary Stent System are packaged with additional patient specific information, which includes:

- A Patient Implant Card that includes both patient and MULTI-LINK VISION Coronary Stent specific information. All patients will be expected to keep this card in their possession at all times for procedure / stent identification.
- A Patient's Guide to Stent Implantation, which includes information on Abbott Vascular, the implant procedure, and the MULTI-LINK VISION Coronary Stent System.

11.0 PATENTS

This product and / or its use are covered by one or more of the following United States Patents: 5,040,548; 5,061,273; 5,154,725; 5,234,002; 5,242,396; 5,350,395; 5,451,233; 5,496,346; 5,514,154; 5,569,295; 5,603,721; 5,636,641; 5,649,952; 5,728,158; 5,735,893; 5,759,192; 5,780,807; 5,868,706; 6,056,776; 6,131,266; 6,165,197; 6,179,810; 6,273,911; 6,309,412; 6,312,459; 6,369,355; 6,419,693; 6,432,133; 6,482,166; 6,485,511; 6,629,991; 6,629,994; 6,651,478; 6,656,220; 6,746,423; 6,827,734; 6,887,219; 6,890,318; 6,908,479; 6,921,411; 6,929,657; 6,939,373. Additional patents pending.

MULTI-LINK VISION is a registered trademark of the Abbott Group of Companies.

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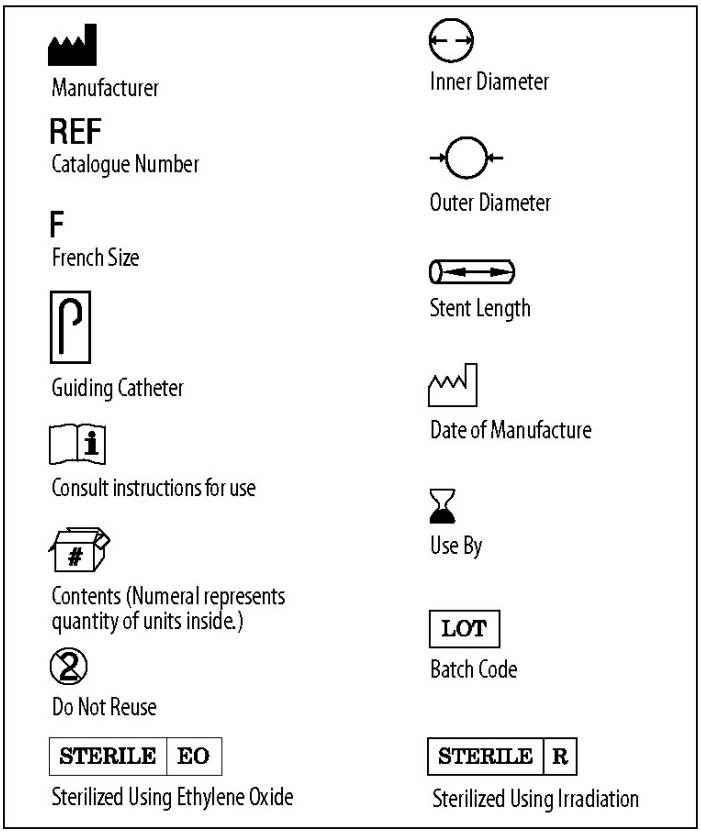
Graphical Symbols for Medical Device Labeling



The XIENCE™ V Everolimus Eluting Coronary Stent System
Instructions for Use

℞ ONLY

Table of Contents

1.0 PRODUCT DESCRIPTION

The XIENCE™ V Everolimus Eluting Coronary Stent System (XIENCE V EECSS or XIENCE V stent system) is a device/drug combination product consisting of either the MULTI-LINK VISION® Coronary Stent System or the MULTI-LINK MINI VISION® Coronary Stent System coated with a formulation containing everolimus, the active ingredient, embedded in a non-erodible polymer.

1.1 Device Component Description

The device component consists of the MULTI-LINK MINI VISION or MULTI-LINK VISION stent mounted onto the MULTI-LINK MINI VISION or MULTI-LINK VISION stent delivery system (SDS) respectively. The device component characteristics are summarized in Table 1-1.

Table 1-1: XIENCE V Stent System Product Description

<table>
<tr><th></th><th>XIENCE V Rapid-Exchange (RX) EECSS</th><th>XIENCE V Over-the-Wire (OTW) EECSS</th></tr>
<tr><td>Available Stent Lengths (mm)</td><td>8, 12, 15, 18, 23, 28</td><td>8, 12, 15, 18, 23, 28</td></tr>
<tr><td>Available Stent Diameters (mm)</td><td>2.5, 2.75, 3.0, 3.5, 4.0</td><td>2.5, 2.75, 3.0, 3.5, 4.0</td></tr>
<tr><td>Stent Material</td><td colspan="2">A medical grade L-605 cobalt chromium (CoCr) alloy MULTI-LINK VISION or MULTI-LINK MINI VISION stent</td></tr>
<tr><td>Drug Component</td><td colspan="2">A conformal coating of a non-erodible polymer loaded with 100 μg/cm^2 of everolimus with a maximum nominal drug content of 181 μg on the large stent (4.0 x 28 mm)</td></tr>
<tr><td>Delivery System Working Length</td><td>143 cm</td><td>143 cm</td></tr>
<tr><td>Delivery System Design</td><td>Single access port to inflation lumen. Guide wire exit notch is located 30 cm from tip. Designed for guide wires ≤ 0.014”.</td><td>Sidearm adaptor provides access to balloon inflation/deflation lumen and guide wire lumen. Designed for guide wires ≤ 0.014”.</td></tr>
<tr><td>Stent Delivery System Balloon</td><td colspan="2">A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length.</td></tr>
<tr><td>Balloon Inflation Pressure</td><td colspan="2">Nominal inflation pressure:
8 atm (811 kPa) for 2.5 and 2.75 mm diameters;
9 atm (912 kPa) for 3.0, 3.5, and 4.0 mm diameters
Rated Burst Pressure (RBP): 16 atm (1621 kPa) for all sizes</td></tr>
<tr><td>Guiding Catheter Inner Diameter</td><td colspan="2">≥ 5 F (0.056”)</td></tr>
<tr><td>Catheter Shaft Outer Diameter (nominal)</td><td>2.5–3.0 mm
Distal: 0.032”
Proximal: 0.026”

3.5–4.0 mm
Distal: 0.035”
Proximal: 0.026”</td><td>2.5 mm
Distal: 0.032”
Proximal: 0.042”

2.75 x 8 – 3.5 x 18
Distal: 0.034”
Proximal: 0.042”

3.5 x 23 – 4.0 x 28
Distal: 0.036”
Proximal: 0.042”</td></tr>
</table>

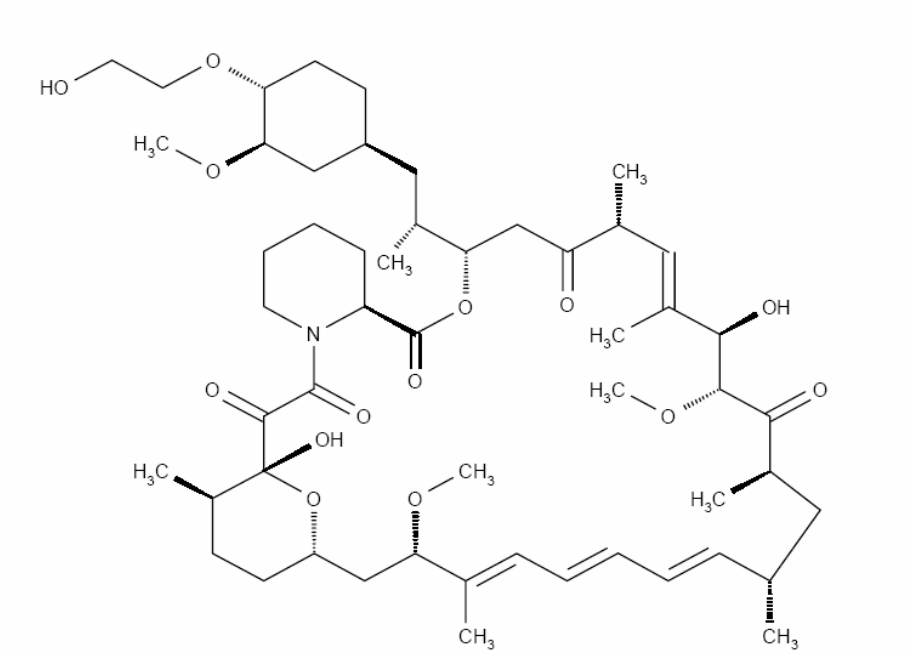
1.2 Drug Component Description

The XIENCE V Everolimus Eluting Coronary Stent (XIENCE V stent) is coated with everolimus (active ingredient), embedded in a non-erodible polymer (inactive ingredient).

1.2.1 Everolimus

Everolimus is the active pharmaceutical ingredient in the XIENCE V stent. It is a novel semi-synthetic macrolide immunosuppressant, synthesized by chemical modification of rapamycin (sirolimus). The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin and the chemical structure is shown in Figure 1-1 below.

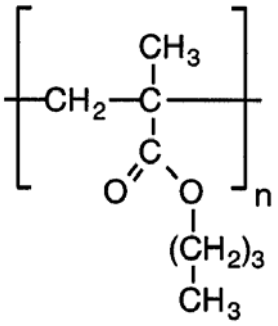
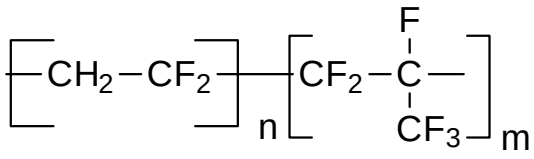
Figure 1-1: Everolimus Chemical Structure



1.2.2. Inactive Ingredients – Non-erodible Polymer

The XIENCE V stent contains inactive ingredients including poly n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus. PBMA is a homopolymer with a molecular weight (Mw) of 264,000 to 376,000 dalton. PVDF-HFP is a non-erodible semi-crystalline random copolymer with a molecular weight (Mw) of 254,000 to 293,000 dalton. The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire PBMA coated stent surface. The drug load is 100 µg/cm^2 for all product sizes. No topcoat layer is used. The polymer chemical structures are shown in Figure 1-2 below.

Figure 1-2: Non-erodible Polymer Chemical Structures

PBMA	PVDF-HFP
	

1.2.3 Product Matrix and Everolimus Content

Table 1-3: XIENCE V EECSS Product Matrix and Everolimus Content

Model Number (RX)	Model Number (OTW)	Nominal Expanded Stent Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (μg)
1009539-08	1009545-08	2.5	8	37
1009540-08	1009546-08	2.75	8	37
1009541-08	1009547-08	3.0	8	37
1009542-08	1009548-08	3.5	8	53
1009543-08	1009549-08	4.0	8	53
1009539-12	1009545-12	2.5	12	56
1009540-12	1009546-12	2.75	12	56
1009541-12	1009547-12	3.0	12	56
1009542-12	1009548-12	3.5	12	75
1009543-12	1009549-12	4.0	12	75
1009539-15	1009545-15	2.5	15	75
1009540-15	1009546-15	2.75	15	75
1009541-15	1009547-15	3.0	15	75
1009542-15	1009548-15	3.5	15	98
1009543-15	1009549-15	4.0	15	98
1009539-18	1009545-18	2.5	18	88
1009540-18	1009546-18	2.75	18	88
1009541-18	1009547-18	3.0	18	88
1009542-18	1009548-18	3.5	18	113
1009543-18	1009549-18	4.0	18	113
1009539-23	1009545-23	2.5	23	113
1009540-23	1009546-23	2.75	23	113
1009541-23	1009547-23	3.0	23	113
1009542-23	1009548-23	3.5	23	151
1009543-23	1009549-23	4.0	23	151
1009539-28	1009545-28	2.5	28	132
1009540-28	1009546-28	2.75	28	132
1009541-28	1009547-28	3.0	28	132
1009542-28	1009548-28	3.5	28	181
1009543-28	1009549-28	4.0	28	181

2.0 INDICATIONS

The XIENCE V Everolimus Eluting Coronary Stent System (XIENCE V stent) is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm.

3.0 CONTRAINDICATIONS

The XIENCE V stent is contraindicated for use in patients:

- Who cannot receive antiplatelet and/or anti-coagulant therapy (see **Section 5.2 Pre- and Post-Procedure Antiplatelet Regimen** for more information)
- With lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system
- With hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers

4.0 WARNINGS

- Ensure that the inner package sterile barrier has not been opened or damaged prior to use.
- Judicious patient selection is necessary because device use has been associated with stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy (see Section 5.2 for important information regarding antiplatelet therapy).

5.0 PRECAUTIONS

5.1 General Precautions

- Stent implantation should only be performed by physicians who have received appropriate training.
- Stent placement should be performed at hospitals where emergency coronary artery bypass graft surgery is accessible.
- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. Long-term outcomes following repeat dilatation of the stent is presently unknown.
- Risks and benefits should be considered in patients with severe contrast agent allergies.
- Care should be taken to control the guiding catheter tip during stent delivery, deployment, and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low-frequency event that current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. Stent thrombosis is frequently associated with myocardial infarction (MI) or death. Data from the XIENCE V SPIRIT family of trials have been prospectively evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic

Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used (see Section 8.2 Stent Thrombosis Definitions and Section 9.4 SPIRIT II and SPIRIT III Pooled Analysis, for more information). In the XIENCE V SPIRIT family of trials analyzed to date, the differences in the incidence of stent thrombosis observed with the XIENCE V stent compared to the TAXUS stent have not been associated with an increased risk of cardiac death, MI, or all-cause mortality. Additional data from longer-term follow-up in the XIENCE V SPIRIT family of trials and analyses of DES-related stent thrombosis are expected and should be considered in making treatment decisions as data become available.

- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the XIENCE V SPIRIT family of trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.
- Orally administered everolimus combined with cyclosporine is associated with increased serum cholesterol and triglycerides levels.

5.2 Pre- and Post-Procedure Antiplatelet Regimen

- In XIENCE V SPIRIT FIRST clinical trial, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 3 months post-procedure (75 mg per day). In XIENCE V SPIRIT II and SPIRIT III clinical trials, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 6 months post-procedure (75 mg per day). Aspirin was administered (a minimum of 75 mg per day) pre-procedure and continued for 1 to 5 years (depending on the study). Based on the case report forms from the SPIRIT II and III randomized clinical trials, approximately 92% of patients remained on dual antiplatelet therapy at 6 months and 62% at 1 year See Section 9.0 – Clinical Studies, for more specific information.
- The optimal duration of dual antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies on sirolimus-eluting or paclitaxel-eluting stents suggest that a longer duration of clopidogrel than was recommended post-procedurally in DES pivotal trials may be beneficial. Current guidelines recommend that patients receive aspirin indefinitely and that clopidogrel therapy be extended to 12 months in patients at low risk of bleeding (ref: ACC/AHA/SCAI PCI Practice Guidelines[1,2]).
- It is very important that the patient is compliant with the post-procedural antiplatelet therapy recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, MI, or death. Prior to percutaneous coronary intervention (PCI), if the patient is required to undergo a surgical or dental procedure that might require early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI treatment of choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risks associated with early discontinuation of antiplatelet therapy. Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should

[1] Smith et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2006; 47: e1-121

[2] King III et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2008; 51:172-209

be monitored carefully for cardiac events. At the discretion of the patient's treating physicians, the antiplatelet therapy should be restarted as soon as possible.

5.3 Multiple Stent Use

A patient’s exposure to drug and polymer is proportional to the number and total length of implanted stents. In the SPIRIT II and III clinical trials, treatment was limited to 36 mm of total stent length in up to two lesions in different epicardial vessels. Use of more than two stents to treat lesions longer than 28 mm has not been evaluated and may increase patient complication risks. Studies evaluating the effects of higher drug doses have not been conducted.

Effects of multiple stenting using XIENCE V stents combined with other drug-eluting stents are also unknown. When multiple drug-eluting stents are required, use only XIENCE V stents in order to avoid potential interactions with other drug-eluting or coated stents.

In addition, only stents composed of similar materials should be implanted in consecutive stent to stent contact to avoid corrosion potential between unrelated materials. Although *in vitro* tests combining L-605 CoCr alloy with 316 L stainless steel did not increase corrosion potential, these studies have not been conducted *in vivo*.

5.4 Brachytherapy

XIENCE V stent safety and effectiveness has not been evaluated in patients with prior target lesion or in-stent restenosis-related brachytherapy.

5.5 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with XIENCE V stent implantation have not been established.

5.6 Use in Special Populations

5.6.1 Pregnancy

Pregnancy Category C. See Section 6.5 – Drug Information, Pregnancy. The XIENCE V stent has not been tested in pregnant women or in men intending to father children. Effects on the developing fetus have not been studied. Effective contraception should be initiated before implanting a XIENCE V stent and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time.

5.6.2 Lactation

See Section 6.6 – Drug Information, Lactation. A decision should be made whether to discontinue nursing prior to stent implantation considering the importance of the stent to the mother.

5.6.3 Gender

No safety- or effectiveness-related gender differences were observed in the individual XIENCE V clinical trials.

5.6.4 Ethnicity

Insufficient subject numbers prevent ethnicity-related analyses on XIENCE V safety and effectiveness.

5.6.5 Pediatric Use

Safety and effectiveness of the XIENCE V stent in pediatric subjects have not been established.

5.6.6 Geriatric Use

Clinical studies of the XIENCE V stent did not suggest that patients age 65 years and over differed with regard to safety and effectiveness compared to younger patients.

5.7 Lesion/Vessel Characteristics

Safety and effectiveness of the XIENCE V stent have not been established for subject populations with the following clinical settings:

- Unresolved vessel thrombus at the lesion site
- Coronary artery reference vessel diameters < 2.5 mm or > 4.25 mm
- Lesion lengths > 28 mm
- Lesions located in saphenous vein grafts
- Lesions located in unprotected left main coronary artery, ostial lesions, chronic total occlusions, lesions located at a bifurcation
- Previously stented lesions
- Diffuse disease or poor flow (TIMI < 1) distal to the identified lesions
- Excessive tortuosity proximal to or within the lesion
- Recent acute myocardial infarction (AMI) or evidence of thrombus in the target vessel
- Moderate or severe lesion calcification
- Multivessel disease
- In-stent restenosis
- Patients with longer than 24 months follow-up.

5.8 Drug Interactions

See Section 6.3 – Drug Information, Interactions with Drugs or Other Substances.
Several drugs are known to affect everolimus metabolism, and other drug interactions may also occur. Everolimus is known to be a substrate for both cytochrome P4503A4 (CYP3A4) and P-glycoprotein. Everolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE V stent because of limited systemic exposure to everolimus eluted from XIENCE V (see Section 6.2 Pharmacokinetics).

Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE V stent in a patient taking a drug with known interaction with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received a XIENCE V Stent.

5.9 Immune Suppression Potential

Everolimus, the XIENCE V stent active ingredient, is an immunosuppressive agent. Immune suppression was not observed in the XIENCE V clinical trials. However, for patients who receive several XIENCE V stents simultaneously, it may be possible for everolimus systemic concentrations to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiency or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. Therefore, consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.

5.10 Lipid Elevation Potential

Oral everolimus use in renal transplant patients was associated with increased serum cholesterol and triglycerides that in some cases required treatment. The effect was seen with both low and high dose prolonged oral therapy in a dose related manner. When used according to the indications for use, exposure to systemic everolimus concentrations from the XIENCE V stent are expected to be significantly lower than concentrations usually obtained in transplant patients. Increased serum cholesterol and triglycerides were not observed in the XIENCE V SPIRIT family of clinical trials.

5.11 Magnetic Resonance Imaging (MRI)

Non-clinical testing has demonstrated that the XIENCE V stent, in single and in overlapped configurations up to 68 mm in length, is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 720 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning or less

The XIENCE V stent should not migrate in this MRI environment. Non-clinical testing at field strengths greater than 3 Tesla has not been performed to evaluate stent migration or heating. MRI at 1.5 or 3 Tesla may be performed immediately following the implantation of the XIENCE V stent.

Stent heating was derived by relating the measured non-clinical, *in vitro* temperature rises in a GE Excite 3 Tesla scanner and in a GE 1.5 Tesla coil to the local specific absorption rates (SARs) in a digitized human heart model. The maximum whole body averaged SAR was determined by validated calculation. At overlapped lengths up to 68 mm, the XIENCE V stent produced a non-clinical maximum local temperature rise of 3ºC at a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for 15 minutes. These calculations do not take into consideration the cooling effects of blood flow.

The effects of MRI on overlapped stents greater than 68 mm in length or stents with fractured struts are unknown.

As demonstrated in non-clinical testing, an image artifact can be present when scanning the XIENCE V stent. MR image quality may be compromised if the area of interest is in the exact same area, or relatively close to, the position of the XIENCE V stent. Therefore, it may be necessary to optimize the MR imaging parameters for the presence of XIENCE V stents.

5.12 Stent Handling

- **Each stent is for single use only.** Do not resterilize or reuse this device. Note the "use by" (expiration) date on the product label.
- **The foil pouch is not a sterile barrier.** The inner header bag (pouch) within the foil pouch is the sterile barrier. **Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile**.
- **Do not remove the stent from the delivery system.** Removal may damage the stent and/or lead to stent embolization. These components are intended to perform together as a system.
- The delivery system should not be used in conjunction with other stents.
- Special care must be taken not to handle or disrupt the stent on the balloon especially during delivery system removal from packaging, placement over the guide wire and advancement through the rotating hemostatic valve adapter and guiding catheter hub.
- **Do not manipulate, touch, or handle the stent** with your fingers, which may cause coating damage, contamination, or stent dislodgement from the delivery balloon.
- Use only the appropriate balloon inflation media (see Section 13.3.3 – Operator's Instructions, Delivery System Preparation). Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in stent deployment.

5.13 Stent Placement

5.13.1 Stent Preparation

- **Do not prepare or pre-inflate the delivery system prior to stent deployment other than as directed.** Use the balloon purging technique described in Section 13.3.3 – Operator's Instructions, Delivery System Preparation.
- **Do not induce negative pressure on the delivery system prior to placing the stent across the lesion.** This may cause dislodgement of the stent from the balloon.
- Use guiding catheters which have lumen sizes that are suitable to accommodate the stent delivery system (see Section 1.1 – Product Description, Device Component Description).

5.13.2 Stent Implantation

- The vessel should be pre-dilated with an appropriate sized balloon. Failure to do so may increase the difficulty of stent placement and cause procedural complications.
- Do not expand the stent if it is not properly positioned in the vessel (see Section 5.14 – Precautions, Stent System Removal).
- Implanting a stent may lead to vessel dissection and acute closure requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).
- Although the safety and effectiveness of treating more than one vessel per coronary artery with XIENCE V stents has not been established, if this is performed, place the

stent in the distal lesion before the proximal lesion in order to minimize dislodgement risk incurred by traversing through deployed stents.

- Stent placement may compromise side branch patency.
- **Do not exceed Rated Burst Pressure (RBP) as indicated on product label.** See Table 14-1, Typical XIENCE V EECSS Compliance. Balloon pressures should be monitored during inflation. Applying pressures higher than specified on the product label may result in a ruptured balloon with possible arterial damage and dissection. The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.
- An unexpanded stent may be retracted into the guiding catheter one time only. An unexpanded stent should not be reintroduced into the artery once it has been pulled back into the guiding catheter. Subsequent movement in and out through the distal end of the guiding catheter should not be performed as the stent may be damaged when retracting the undeployed stent back into the guiding catheter.
- Should **any resistance** be felt **at any time** during coronary stent system withdrawal, the stent delivery system and guiding catheter should be **removed as a single unit** (see Section 5.14 – Precautions, Stent System Removal).
- Stent retrieval methods (i.e., using additional wires, snares, and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Although the stent delivery system balloon is strong enough to expand the stent without rupture, a circumferential balloon tear distal to the stent and prior to complete stent expansion, could cause the balloon to become tethered to the stent, requiring surgical removal. In case of balloon rupture, it should be withdrawn and, if necessary, a new dilatation catheter exchanged over the guide wire to complete the expansion of the stent.
- Ensure the stented area covers the entire lesion/dissection site and that no gaps exist between stents.

5.14 Stent System Removal

Should **any resistance** be felt **at any time** during either lesion access or removing the delivery system post-stent implantation, the stent delivery system and the guiding catheter should be **removed as a single unit.**

When removing the delivery system and guiding catheter as a single unit, the following steps should be executed under direct visualization using fluoroscopy:

- Confirm complete balloon deflation. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to the guiding catheter position. In some cases it may be necessary to slightly retract the guiding catheter in order to prevent unplanned guiding catheter movement and subsequent vessel damage. In cases where unplanned guiding catheter movement has occurred, a coronary tree angiographic assessment should be undertaken to ensure that there is no damage to the coronary vasculature.
- DO NOT retract the delivery system into the guiding catheter.
- Position the proximal balloon marker just distal to guiding catheter tip.
- Advance the guide wire into the coronary anatomy as far distally as safely possible.
- Tighten the rotating hemostatic valve to secure the delivery system to the guiding catheter, and remove the guiding catheter and delivery system as a **single unit**.

Failure to follow these steps and/or applying excessive force to the delivery system can potentially result in loss or damage to the stent and/or delivery system components.

If it is necessary to retain guide wire position for subsequent artery/lesion access, leave the guide wire in place and remove all other system components.

Stent retrieval methods (i.e., additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include, but are not limited to, bleeding, hematoma, or pseudoaneurysm.

5.15 Post-Procedure

- When **crossing a newly deployed stent** with an intravascular ultrasound (IVUS) catheter, a coronary guide wire, a balloon catheter or delivery system, exercise care to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Antiplatelet therapy should be administered post-procedure (see Section 5.2 Pre- and Post-Procedure Antiplatelet Regimen and Section 9.0 Clinical Studies). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.
- If the patient requires imaging, see Section 5.11 – Precautions, Magnetic Resonance Imaging (MRI).

6.0 DRUG INFORMATION

6.1 Mechanism of Action

The mechanism by which the XIENCE V Stent inhibits neointimal growth as seen in pre-clinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 Rapamycin Associated Protein), also known as mTOR (mammalian Target Of Rapamycin), leading to inhibition of cell metabolism, growth, and proliferation by arresting the cell cycle at the late G1 stage.

6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent

Everolimus pharmacokinetics (PK) when eluted from the XIENCE V Stent post-implantation has been evaluated in three different substudies in three different geographies. The SPIRIT III clinical trial design includes a pharmacokinetic substudy in the US randomized arm and a pharmacokinetic substudy in the Japanese non-randomized arm. The third PK substudy was conducted as part of the SPIRIT II clinical trial at sites in Europe, India, and New Zealand. Whole blood everolimus PK parameters determined from subjects receiving the XIENCE V stent are provided in Table 6-1.

Table 6-1: Whole Blood Everolimus Pharmacokinetic Parameters in Patients Following XIENCE V Stent Implantation

SPIRIT III RCT and 4.0 Arm							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{0-t}[a] (ng.h mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)[a]
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=3[b])	88 µg	0.050 (0.50-1.88)	0.3867 ± 0.09866		5.31 ± 4.114		
3.5-4.0 x 28 mm (n=6[c])	181 µg	0.50 (0.07-1.00)	1.175 ± 0.6817	79.08 ± 57.24	23.73 ± 13.63	44.00 ± 28.67	5.130 ± 2.114
SPIRIT III Japanese Arm							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=6)	88 µg	1.00 (0.50-1.02)	0.5017 ± 0.1398	45.22 ± 35.08	5.049 ± 2.138	12.98 ± 7.078	9.286 ± 6.069
3.5-4.0 x 18 mm (n=4[b])	113 µg	0.51 (0.50-0.53)	0.6500 ± 0.08756	53.57 ± 19.34	11.02 ± 4.002	19.97 ± 7.890	6.471 ± 2.807
SPIRIT II Clinical Trial							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{last} (ng.h/mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)[a]
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=13)	88 µg	0.50 (0.13-2.17)	0.4369 ± 0.1507	54.08 ± 35.78	8.255 ± 5.863	19.60 ± 15.30	8.066 ± 6.443
3.5-4.0 x 18 mm (n=4[c])	113 µg	0.50 (0.50-0.50)	0.5850 ± 0.2630	47.60 ± 62.13	42.54 ± 58.83	22.79 ± 31.47	16.96 ± 13.07
3.5-4.0 x 28 mm (n=4)	181 µg	0.46 (0.17-1.00)	0.7925 ± 0.1406	103.4 ± 64.17	28.07 ± 13.18	52.71 ± 27.40	5.332 ± 5.048

[a] Accurate determination not possible due to rapid disappearance of everolimus from the blood
[b] n= 5 for $t_{1/2}$ and CL
[c] n= 3 for $t_{1/2}$ and CL
t_{max}(h)= time to maximum concentration
C_{max}= maximum observed blood concentration
$t_{1/2}$ (h)= terminal phase half-life
AUC_{0-t} or AUC_{last} = the area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration
$AUC_{(0-\infty)}$ = the area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time
CL= total blood clearance

In all subjects, the maximum time to everolimus disappearance was 168 hours; however, 1 subject in the SPIRIT II clinical trial had detectable levels at 30 days. In all 3 studies, the C_{max} value never reached the minimum therapeutic value of 3.0 ng/mL necessary for effective systemic administration to prevent organ rejection. The PK parameters representing elimination; $t_{½}$, AUC_{0-t}, AUC_{last}, AUC_{∞}, and CL could also not be determined accurately due to rapid everolimus disappearance from blood. These types of results have been seen with other drug-eluting stents.

Everolimus disappearance from circulation following XIENCE V stent implantation should further limit systemic exposure and adverse events associated with long-term systemic administration at therapeutic levels. Despite limited systemic exposure to everolimus, local arterial delivery has been demonstrated in pre-clinical studies.

6.3 Interactions with Drugs or Other Substances

Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the gut wall and liver and is a substrate for the countertransporter P-glycoprotein. Therefore, absorption and subsequent elimination of everolimus may be influenced by drugs that also affect this pathway. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE V stent because of limited systemic exposure to everolimus eluted from XIENCE V (see Section 6.2 Pharmacokinetics). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE V stent in a subject taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the drugs/foods[3] listed below. Medications that are strong inhibitors of CYP3A4 might reduce everolimus metabolism *in vivo*. Hence, co-administration of strong inhibitors of CYP3A4 may increase the blood concentrations of everolimus.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavor, erythromycin, clarithromycin, fluconazole, calcium channel blockers)
- Inducers of CYP3A4 isozyme (rifampin, rifabutin, carbamazepin, phenobarbital, phenytoin)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- Digoxin
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra®) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit juice

6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

A 26-week carcinogenicity study was conducted to evaluate the carcinogenic potential of XIENCE V stents following subcutaneous implantation in transgenic mice. During the course of the study, there were no abnormal clinical observations that suggested a carcinogenic effect of the test group (XIENCE V stent). The test group did not demonstrate an increased incidence of neoplastic lesions when compared to the negative control group. However, the positive control and the experimental positive control groups demonstrated notable increases in the incidence of neoplastic lesions compared to either the test or the negative control group. Based on the results of this study, the XIENCE V stent does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

Genotoxicity studies were conducted on the XIENCE V stent in mammalian cells and bacteria. These studies included gene mutations in bacteria (Ames Test), gene mutations in mammalian cells (chromosomal aberration), test for clastogenicity in mammalian cells, and mammalian erythrocyte micronucleus test. Based on the results of these studies, the XIENCE V stent is not genotoxic.

[3] Certican® Investigator's Brochure. Novartis Pharmaceutical Corporation

In addition, a reproductive toxicity (teratology) study was conducted to demonstrate that implantation of XIENCE V stents in female Sprague-Dawley rats does not affect their fertility or reproductive capability and shows a lack of any reproductive toxicity on their offspring. The XIENCE V stent did not affect the fertility or reproductive capability of female Sprague-Dawley rats. There was no statistical difference between the test article (XIENCE V stent) and the control system in terms of any of the evaluated parameters. The test article had no effect on litter size and caused no increase of in utero mortality. Additionally, the XIENCE V stent did not cause any reproductive toxicity in the offspring in this study.

6.5 Pregnancy

Pregnancy Category C: There are no adequate everolimus or XIENCE V stent related studies in pregnant women. Effects of the XIENCE V stent on prenatal and postnatal rat development were no different than the controls. When administered at oral doses of 0.1 mg/kg or above, everolimus showed effects on prenatal and postnatal rat development limited to slight body weight changes and fetal survival without any specific toxic potential.

Effective contraception should be initiated before implanting a XIENCE V stent and continued for one year post-implantation. The XIENCE V stent should be used in pregnant women only if potential benefits justify potential risks.

Safety of the XIENCE V stent has not been evaluated in males intending to father children.

6.6 Lactation

It is unknown whether everolimus is distributed in human milk. Also, everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to XIENCE V stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

7.0 OVERVIEW OF CLINICAL STUDIES

Principal XIENCE V safety and effectiveness information is derived from the SPIRIT III clinical trial and is supported by the SPIRIT FIRST and SPIRIT II clinical trials. These studies evaluated XIENCE V EECSS performance in subjects with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and listed in Table 7-1.

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS EXPRESS^2™ Paclitaxel Eluting Coronary Stent System (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consisted of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Enrollment is complete in the RCT and the Japan arm.

The SPIRIT III RCT was a prospective, randomized (2:1; XIENCE V:TAXUS), active-controlled, single-blinded, multi-center, clinical trial in the US designed to evaluate the safety and efficacy

of the XIENCE V stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 3.75 mm. The RCT study was designed to enroll 1,002 subjects at up to 80 sites in the US. The primary endpoint in the RCT was in-segment late loss at 240 days, and the co-primary endpoint was ischemia-driven target vessel failure (TVF, defined as the composite of cardiac death, MI, or clinically-driven TVR) at 270 days. Other secondary endpoints included clinical outcomes of all the subjects (30, 180, 270 days and annually from 1 to 5 years), as well as angiographic results and intravascular ultrasound (IVUS) results at 240 days. Follow-up through 1 year is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT III 4.0 mm arm was a prospective, multi-center, single-arm registry designed to evaluate the XIENCE V stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD > 3.75 mm to ≤ 4.25 mm. This study was designed to enroll up to 80 subjects at up to 80 sites in the US. Enrolled subjects were scheduled for clinical follow-up at 30, 180, 240, and 270 days and annually from 1 to 5 years, with angiographic follow-up at 240 days. The primary endpoint was in-segment late loss at 240 days compared to the TAXUS arm from the SPIRIT III RCT. Follow-up through 1 year is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subset derived from the RCT[4] and Japan non-randomized arm. Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan).

The SPIRIT II clinical trial was a randomized, single-blind, active-control, multi-center clinical evaluation. Subject eligibility criteria were similar to the SPIRIT III clinical trial and enrollment duration overlapped between studies. In this study, 300 subjects (3:1 randomization XIENCE V: TAXUS) were enrolled at 28 sites outside the United States. The primary endpoint was in-stent late loss at 6 months. Secondary endpoints included clinical outcomes at 30, 180, 270 days and annually from 1 to 5 years; angiographic results at 180 days and 2 years; and IVUS results at 180 days and 2 years. Clinical follow-up through 2 years is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT FIRST clinical trial was a randomized, single-blind, controlled, multi-center first-in-man study. This trial was the first human study to evaluate the XIENCE V stent safety and performance. Sixty subjects [XIENCE V stent (n=28) and MULTI-LINK VISION bare metal control stent (n=32)] were enrolled at 9 sites in Europe. The primary endpoint was in-stent late loss at 6 months on the per-treatment evaluable population, and the major secondary endpoint was the percent in-stent volume obstruction (% VO) at 6 months based on IVUS analysis of the per-treatment evaluable population. Follow-up through 3 years is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

Table 7-1 summarizes the clinical trial designs for the SPIRIT family of trials.

[4] Includes one subject from the 4.0 mm non-randomized arm

Table 7-1: XIENCE V SPIRIT Clinical Trial Designs

	SPIRIT III clinical trial		SPIRIT II clinical trial	SPIRIT FIRST clinical trial
	RCT	**Registries**		
Study Type/Design	• Multi-center • Randomized • Single-blinded • Active-Control	• Multi-center • Single-arm • Open-label	• Multi-center • Randomized • Single-blinded • Active-Control	• Multi-center • Randomized • Single-blinded • Control
Number of Subjects Enrolled	Total: 1,002 XIENCE V: 668 TAXUS Control: 334	Total: 168 4.0 mm: 80 Japan: 88*	Total: 300 XIENCE V: 225 TAXUS Control: 75	Total: 60 XIENCE V: 30 VISION Control: 30
Treatment	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Single *de novo* lesion
Lesion Size	RVD: ≥ 2.5 ≤ 3.75 mm Length: ≤ 28 mm	4.0 mm RVD: > 3.75 ≤ 4.25 mm Length: ≤ 28 mm	RVD: ≥ 2.5 ≤ 4.25 mm Length: ≤ 28 mm	RVD: 3 mm Length: ≤ 12 mm
		Japan RVD: ≥ 2.5 ≤ 4.25 mm Length: ≤ 28 mm		
Stent Sizes (XIENCE V)	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 18, 28 mm	4.0 mm Diameter: 4.0 mm Length: 8, 18, 28 mm Japan Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 3.0 mm Length: 18 mm
Post-procedure Antiplatelet Therapy	Clopidogrel 6 months minimum (or ticlopidine per site standard), Aspirin 5 years	4.0 mm: same as RCT Japan: Ticlopidine 3 months, Aspirin 5 years	Clopidogrel 6 months minimum (or ticlopidine per site standard), Aspirin 1 year	Clopidogrel 3 months minimum (or ticlopidine per site standard), Aspirin 1 year
Primary Endpoint	In-segment late loss at 240-days	In-segment late loss at 240-days	In-stent late loss at 180-days	In-stent late loss at 180-days
Co-Primary Endpoint	TVF at 270-days	None	None	None
Clinical Follow-up	30, 180, 240, 270 days, 1 to 5 years	30, 180, 240, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years
Angiographic Follow-up	240 days (N=564)	240 days (All registry)	180-day (all), 2-years (N=152)	180-days, 1-year (all)
IVUS Follow-up	240 days (N=240)	240 days (Japan only)	180-day, 2-years (N=152)	180-days, 1-year (all)
PK Study	US: Minimum 15 subjects with single lesion, maximum 20 with dual lesions Japan: Minimum 10 subjects with single lesion, maximum 20 with dual lesions		Minimum 15 subjects with single lesion, maximum 20 with dual lesions	None
Status	One year reported; 2, 3, 4 and 5 years planned		One and 2 years reported; 3, 4 and 5 years planned	One, 2, and 3 years reported; 4 and 5 years planned

*Only pharmacokinetic substudy results included (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent).

8.0 ADVERSE EVENTS

8.1 Observed Adverse Events

Principal adverse event information is derived from SPIRIT III, SPIRIT II and SPIRIT FIRST clinical trials and is shown in Table 8.1-1 and 8.1-2. Within these tables, the Intent-to-Treat population includes all subjects randomized, while the Per-Treatment Evaluable population includes only those subjects who received a study device at the target lesion with no major procedure protocol deviations except deviations relating to the treatment arm, for whom follow-up data are available. See also Section 8.3 – Adverse Events, Potential Adverse Events. See Section 9.0 – Clinical Studies for more complete study design descriptions and results.

Table 8.1-1: SPIRIT III, II and FIRST:
Principal Adverse Events From Post-Procedure to 1 Year

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
In Hospital							
TVF[1]	0.9% (6/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)	0.0% (0/28)
MACE[2]	0.9% (6/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)	0.0% (0/28)
All Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Non-Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
MI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
QMI	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
NQMI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
Cardiac Death or MI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
Ischemia-Driven Revascularization	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)	0.0% (0/28)
Ischemia-Driven TLR	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)	0.0% (0/28)
Ischemia-Driven Non-TLR TVR	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Stent Thrombosis[3] (Per Protocol)	0.3% (2/669)	0.0% (0/330)	1.4% (1/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
9 Months[4]							
TVF[1]	7.6% (50/657)	9.7% (31/320)	5.9% (4/68)	4.5 (10/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
MACE[2]	5.0% (33/657)	8.8% (28/320)	5.9% (4/68)	2.7% (6/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
All Death	1.1% (7/658)	0.9% (3/321)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.6% (4/658)	0.6% (2/321)	1.5% (1/68)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	**TAXUS (N=333)**	**XIENCE V 4.0 mm Arm (N=69)**	**XIENCE V (N=223)**	**TAXUS (N=77)**	**XIENCE V (N=27)**	**VISION (N=29)**
Non-Cardiac Death	0.5% (3/658)	0.3% (1/321)	0.0% (0/68)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
MI	2.3% (15/657)	3.1% (10/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
QMI	0.2% (1/657)	0.0% (0/320)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	2.1% (14/657)	3.1% (10/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death or MI	2.9% (19/657)	3.8% (12/320)	5.9% (4/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
Ischemia-Driven Revascularization	5.3% (35/657)	6.6% (21/320)	1.5% (1/68)	3.6% (8/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)
Ischemia-Driven TLR	2.7% (18/657)	5.0% (16/320)	1.5% (1/68)	1.8% (4/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)
Ischemia-Driven TVR, non TLR TVR	2.9% (19/657)	4.1% (13/320)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis[3]							
Protocol	0.6% (4/654)	0.0% (0/319)	1.5% (1/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
1 Year[5]							
TVF[1]	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	4.5% (10/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)
MACE[2]	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	2.7% (6/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)
All Death	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.8% (5/655)	0.9% (3/321)	1.5% (1/68)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Non Cardiac Death	0.5% (3/655)	0.3% (1/321)	0.0% (0/68)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
MI	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)
QMI	0.3% (2/653)	0.3% (1/320)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	2.5% (16/653)	3.8% (12/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
Cardiac Death or MI	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)
Ischemia-Driven Revascularization	6.1% (40/653)	7.5% (24/320)	1.5% (1/68)	3.6% (8/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
Ischemia-Driven TLR	3.4% (22/653)	5.6% (18/320)	1.5% (1/68)	1.8% (4/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
Ischemia-Driven non-TLR TVR	3.1% (20/653)	4.4% (14/320)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis[3]							
Per Protocol	0.8% (5/647)	0.6% (2/317)	1.5% (1/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
ARC (Definite+Probable)	1.1% (7/648)	0.6% (2/317)	0.0% (0/67)	0.0% (0/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)

Notes:

- In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- This table includes revascularizations on any target vessel(s)/lesion(s) for subjects with two target vessels / lesions treated.
- One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- SPIRIT II and III based on Intent to Treat Population (all subjects randomized, regardless of the treatment they actually received).
- SPIRIT FIRST based on per-treatment evaluable population [a subset of subjects in the full analysis set, who had no bailout and no major protocol deviations other than those relating to treatment arm (randomized versus actually received)].
- Revascularization includes TLR and Non-TLR TVR.
- Q wave MI for all SPIRIT Trials is defined as the development of new pathological Q wave on the ECG.
- Non Q wave MI for SPIRIT III is defined as the elevation of CK levels to greater than or equal to 2 times the upper limit of normal with elevated CKMB in the absence of new pathological Q waves.
- Non Q wave MI for SPIRIT II is defined as a typical rise and fall of CKMB with at least one of the following: Ischemia symptoms, ECG changes indicative of ischemia (ST segment elevation or depression), or coronary artery intervention.
  - If non procedural/spontaneous MI, CKMB is greater than or equal to 2 times upper limit of normal
  - If post PCI, CKMB is greater than or equal to 3 times upper limit of normal
  - If post CABG, CKMB is greater than or equal to 5 times upper limit of normal
- Non Q wave MI for SPIRIT FIRST is defined (WHO definition) as the elevation of post procedure CK levels to greater than or equal to 2 times the upper normal limit with elevated CKMB in the absence of new pathological Q waves.
- Non Q wave MI for SPIRIT FIRST is defined (ESC/ACC definition) as for non procedural, CKMB elevation greater than or equal to 2 times the upper normal limit, for post PCI, CKMB elevation greater than or equal to three times the upper normal limit, and for post CBAG, CKMB elevation greater than or equal to five times the upper normal limit.

[1] TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion.
[2] MACE includes cardiac death, MI and ischemia-driven TLR.
[3] See Section 8.2 – Stent Thrombosis Definitions.
[4] SPIRIT III and SPIRIT FIRST includes 14 day window. SPIRIT III includes 9 month events identified at the 1 year follow-up.
[5] SPIRIT III and SPIRIT FIRST includes 28 day window.

Table 8.1-2: SPIRIT III, II and FIRST: Principal Adverse Events from Latest Follow-up

	SPIRIT III *1 Year*[4]			SPIRIT II *2 Year*[4]		SPIRIT FIRST *3 Year*[4]	
	XIENCE V (N=669)	**TAXUS (N=333)**	**XIENCE V 4.0 mm Arm (N=69)**	**XIENCE V (N=223)**	**TAXUS (N=77)**	**XIENCE V (N=27)**	**VISION (N=29)**
TVF[1]	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	10.0% (21/211)	12.3% (9/73)	15.4% (4/26)	32.1% (9/28)
MACE[2]	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	6.6% (14/211)	11.0% (8/73)	15.4% (4/26)	25.0% (7/28)
All Death	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	3.7% (8/218)	6.5% (5/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.8% (5/655)	0.9% (3/321)	1.5% (1/68)	0.5% (1/218)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Non-Cardiac Death	0.5% (3/655)	0.3% (1/321)	0.0% (0/68)	3.2% (7/218)	5.2% (4/77)	0.0% (0/26)	0.0% (0/28)
MI	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	2.8% (6/211)	5.5% (4/73)	7.7% (2/26)	0.0% (0/28)
QMI	0.3% (2/653)	0.3% (1/320)	0.0% (0/68)	0.0% (0/211)	0.0% (0/73)	3.8% (1/26)	0.0% (0/28)
NQMI	2.5% (16/653)	3.8% (12/320)	4.4% (3/68)	2.8% (6/211)	5.5% (4/73)	3.8% (1/26)	0.0% (0/28)
Cardiac Death or MI	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	3.3% (7/211)	5.5% (4/73)	7.7% (2/26)	0.0% (0/28)
Ischemia-Driven Revascularization	6.1% (40/653)	7.5% (24/320)	1.5% (1/68)	7.1% (15/211)	9.6% (7/73)	7.7% (2/26)	32.1% (9/28)
Ischemia-Driven TLR	3.4% (22/653)	5.6% (18/320)	1.5% (1/68)	3.8% (8/211)	6.8% (5/73)	7.7% (2/26)	25.0% (7/28)
Ischemia-Driven non-TLR TVR	3.1% (20/653)	4.4% (14/320)	0.0% (0/68)	3.8% (8/211)	4.1% (3/73)	0.0% (0/26)	10.7% (3/28)
Stent Thrombosis[3]							
Per Protocol	0.8% (5/647)	0.6% (2/317)	1.5% (1/67)	1.9% (4/211)	1.4% (1/73)	0.0% (0/26)	0.0% (0/28)
ARC (Definite+Probable)	1.1% (7/648)	0.6% (2/317)	0.0% (0/67)	0.9% (2/211)	1.4% (1/73)	0.0% (0/26)	0.0% (0/28)

Notes:

- In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- This table includes revascularizations on any target vessel(s)/lesion(s) for subjects with two target vessels / lesions treated.
- One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- SPIRIT II and III based on Intent to Treat Population (all subjects randomized, regardless of the treatment they actually received).
- SPIRIT FIRST based on per-treatment evaluable population [a subset of subjects in the full analysis set, who had no bailout and no major protocol deviations other than those relating to treatment arm (randomized versus actually received)].
- Revascularization includes TLR and Non-TLR TVR.

[1] TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion.
[2] MACE includes cardiac death, MI and ischemia-driven TLR.
[3] See Section 8.2 – Stent Thrombosis Definitions.
[4] SPIRIT III, SPIRIT II and SPIRIT FIRST includes 28 day window.

8.2 Stent Thrombosis Definitions

Protocol defined stent thrombosis (ST) was categorized as acute (< 1 day), subacute (1 - 30 days) and late (> 30 days) and was defined as any of the following[5]:

- Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis (angiographic appearance of thrombus within or adjacent to a previously treated target lesion)
- In the absence of angiography, any unexplained death, or acute MI (ST segment elevation or new Q-wave)[6] in the distribution of the target lesion within 30 days

All stent thrombosis events were also classified using the ST definitions proposed by the Academic Research Consortium (ARC)[7]. This was performed by an independent event committee blinded to the treatment group of the individual subject. The committee categorized each incident of ST by timing and level of probability (definite, probable, possible), and relation to the original index procedure (primary, secondary after revascularization). These categories are defined as follows:

Timing:

- Early ST: 0 to 30 days post stent implantation
- Late ST: 31 days to 1 year post stent implantation
- Very late ST: > 1 year post stent implantation

Level of probability:

- Definite ST - considered to have occurred by either angiographic or pathologic confirmation
- Probable ST - considered to have occurred after intracoronary stenting in the following cases:
    1. Any unexplained death within the first 30 days.
    2. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.
- Possible ST - considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up[8]

8.3 Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with percutaneous coronary and treatment procedures including coronary stent use in native coronary arteries include, but are not limited to:

- Abrupt closure
- Access site pain, hematoma, or hemorrhage
- Acute myocardial infarction

[5] For SPIRIT FIRST Stent Thrombosis is defined as total occlusion by angiography at the stent site with abrupt onset of symptoms, elevated biochemical markers, and ECG changes consistent with MI.

[6] Non-specific ST/T changes, and cardiac enzyme elevations do not suffice.

[7] Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circ* 2007;115:2344-51.

[8] All data within this Instructions for Use is presented as definite + probable only.

- Allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers; and drug reactions to antiplatelet drugs or contrast agent
- Aneurysm
- Arterial perforation and injury to the coronary artery
- Arterial rupture
- Arteriovenous fistula
- Arrhythmias, atrial and ventricular
- Bleeding complications, which may require transfusion
- Cardiac tamponade
- Coronary artery spasm
- Coronary or stent embolism
- Coronary or stent thrombosis
- Death
- Dissection of the coronary artery
- Distal emboli (air, tissue or thrombotic)
- Emergent or non-emergent coronary artery bypass graft surgery
- Fever
- Hypotension and/or hypertension
- Infection and pain at insertion site
- Injury to the coronary artery
- Ischemia (myocardial)
- Myocardial infarction (MI)
- Nausea and vomiting
- Palpitations
- Peripheral ischemia (due to vascular injury)
- Pseudoaneurysm
- Renal failure
- Restenosis of the stented segment of the artery
- Shock/pulmonary edema
- Stroke/cerebrovascular accident (CVA)
- Total occlusion of coronary artery
- Unstable or stable angina pectoris
- Vascular complications including at the entry site which may require vessel repair
- Vessel dissection

Adverse events associated with daily oral administration of everolimus to organ transplant patients include but are not limited to:

- Abdominal pain
- Acne
- Anemia
- Coagulopathy
- Diarrhea
- Edema
- Hemolysis
- Hypercholesterolemia
- Hyperlipidemia

- Hypertension
- Hypertriglyceridemia
- Hypogonadism male
- Infections: wound infection, urinary tract infection, pneumonia, pyelonephritis, sepsis and other viral, bacterial and fungal infections
- Leukopenia
- Liver function test abnormality
- Lymphocele
- Myalgia
- Nausea
- Pain
- Rash
- Renal tubular necrosis
- Surgical wound complication
- Thrombocytopenia
- Venous thromboembolism
- Vomiting

There may be other potential adverse events that are unforeseen at this time.

9.0 XIENCE V SPIRIT FAMILY OF CLINICAL TRIALS

9.1 SPIRIT III Pivotal Clinical Trial

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS EXPRESS^{2}™ Paclitaxel Eluting Coronary Stent System (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consists of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy. Enrollment is complete in the RCT and the Japan arm.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subject subset derived from the RCT[9] and Japan non-randomized arm (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan). Venous blood was drawn at regular intervals for pharmacokinetics analysis of total blood everolimus level at pre-determined sites.

9.1.1 SPIRIT III Randomized Clinical Trial (RCT)

Primary Objective: The objective of the SPIRIT III RCT was to demonstrate the non-inferiority in in-segment late loss at 240 days and target vessel failure at 270 days of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with a reference vessel diameter (RVD) ≥ 2.5 mm to ≤ 3.75 mm. If non-inferiority of in-segment late loss was demonstrated, it was pre-specified that testing for superiority could be conducted.

[9] Includes one subject from the 4.0 mm non-randomized arm

Design: The SPIRIT III RCT was a prospective, 2:1 (XIENCE V:TAXUS) randomized, active-controlled, single-blinded, parallel, multi-center non-inferiority evaluation of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 3.75 mm. Given the available XIENCE V stent lengths of 8, 18 and 28 mm for this trial, in the XIENCE V arm, treatment of a target lesion > 22 mm and ≤ 28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent. In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage. The RCT was designed to enroll 1,002 subjects at up to 80 sites in the United States.

All subjects had clinical follow-up at 30, 180, and 270 days and annually from 1 to 5 years. A pre-specified subgroup of 564 subjects had angiographic follow-up at 240 days. Of these 564, 240 subjects had IVUS at baseline and 240 days. Subjects that received a bailout stent also had IVUS at baseline and angiographic and IVUS follow-up at 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

Demographics: The mean age was 63.2 years for the XIENCE V arm and 62.8 for the TAXUS arm. The XIENCE V had 70.1% (469/669) males and the TAXUS arm had 65.7% (218/332) males. The XIENCE V arm had 32.3% (215/666) of subjects with prior cardiac interventions and the TAXUS arm had 29.5% (98/332). The XIENCE V arm had 29.6% (198/669) of subjects with a history of diabetes and the TAXUS arm had 27.9% (92/330). The XIENCE V had 15.4% (103/669) of subjects with a lesion treated in two vessels and TAXUS had 15.4% (51/332). The XIENCE V arm had 8.1% (54/669) of subjects with planned stent overlap. The XIENCE V arm had 8.6% (57/666) of subjects with a history of prior CABG while the TAXUS arm had 3.6% (12/332) (p = 0.0033). The XIENCE V arm had 18.7% (123/657) of subjects with a history of unstable angina while the TAXUS arm had 25.1% (82/327) (p=0.0243). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

Results: The results are presented in Table 9.1.1-1 (Primary endpoints), Table 9.1.1-2 (Clinical Results), Table 9.1.1-3 (Angiographic and IVUS Results), Figure 9.1.1-1 (TVF Free Survival) and Table 9.1.1-4 (ARC-Defined Stent Thrombosis). These analyses are based on the intent to treat population.

The co-primary endpoint of in-segment late loss at 240 days was met with measurements of 0.14 ± 0.41 mm (301) for the XIENCE V arm and 0.28 ± 0.48 mm (134) for the TAXUS arm (p < 0.0001 for non-inferiority). In a prespecified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-segment late loss at 240 days (p = 0.0037).

The co-primary endpoint of ischemia-driven TVF through 284 days was met with rates of 7.6% (50/657) for the XIENCE V arm and 9.7% (31/320) for the TAXUS arm (p < 0.001 for non-inferiority).

Table 9.1.1-1: SPIRIT III RCT Primary Endpoints Results

Measurements	XIENCE V (N=669) (M=376)	TAXUS (N=333) (M=188)	Difference [95% CI]	Non-Inferiority P-Value	Superiority P-Value
8 Month[1] Late Loss, In-segment (mm)	0.14 ± 0.41 (301)	0.28 ± 0.48 (134)	-0.14 [-0.23, -0.05][2]	<0.0001[3]	0.0037[4]
9 Month[5] Target Vessel Failure[6]	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%][2]	<0.0001[7]	Not Pre-specified

Notes:

- N is the total number of subjects; M is the total number of analysis lesions.
- One in SPIRIT III TAXUS arm subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Analysis results include 9 month events identified at the 1 year follow-up.

[1] 8 month time frame includes follow-up window (240 + 28 days).
[2] By normal approximation.
[3] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.025 significance level.
[4] Two-sided p-value by superiority test using two-sample T-test, to be compared at a 0.05 significance level.
[5] 9 month time frame includes follow-up window (270 + 14 days).
[6] TVF is defined as hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[7] One sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 5.5%, to be compared at a 0.05 significance level.

Table 9.1.1-2: SPIRIT III RCT Clinical Results

	OUTCOMES AT 9 MONTHS			OUTCOMES AT 1 YEAR (latest available follow-up)		
	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI][1]	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI][1]
COMPOSITE EFFICACY & SAFETY						
TVF[2]	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%]	8.6% (56/653)	11.3% (36/320)	-2.67% [-6.75%, 1.40%]
MACE[3]	5.0% (33/657)	8.8% (28/320)[7]	-3.73% [-7.24%, -0.21%]	6.0% (39/653)	10.3% (33/320)	-4.34% [-8.14%, -0.54%]
EFFICACY						
Ischemia-Driven TLR	2.7% (18/657)	5.0% (16/320)	-2.26% [-4.95%, 0.43%]	3.4% (22/653)	5.6% (18/320)	-2.26% [-5.13%, 0.62%]
TLR, CABG	0.2% (1/657)	0.0% (0/320)	0.15% [Assump. not met]	0.3% (2/653)	0.0% (0/320)	0.31% [Assump. not met]
TLR, PCI	2.6% (17/657)	5.0% (16/320)	-2.41% [-5.09%, 0.27%]	3.1% (20/653)	5.6% (18/320)	-2.56% [-5.41%, 0.29%]
Ischemia-Driven non-TLR TVR	2.9% (19/657)	4.1% (13/320)	-1.17% [-3.68%, 1.34%]	3.1% (20/653)	4.4% (14/320)	-1.31% [-3.91%, 1.29%]
non-TLR TVR, CABG	0.5% (3/657)	0.6% (2/320)	-0.17% [Assump. not met]	0.6% (4/653)	0.6% (2/320)	-0.01% [Assump. not met]
non-TLR TVR, PCI	2.4% (16/657)	3.4% (11/320)	-1.00% [-3.32%, 1.32%]	2.5% (16/653)	3.8% (12/320)	-1.30% [-3.70%, 1.10%]
SAFETY						
All Death	1.1% (7/658)	0.9% (3/321)	0.13% [Assump. not met]	1.2% (8/655)	1.2% (4/321)	-0.02% [Assump. not met]
Cardiac Death	0.6% (4/658)	0.6% (2/321)	-0.02% [Assump. not met]	0.8% (5/655)	0.9% (3/321)	-0.17% [Assump. not met]
Non-Cardiac Death	0.5% (3/658)	0.3% (1/321)	0.14% [Assump. not met]	0.5% (3/655)	0.3% (1/321)	0.15% [Assump. not met]
MI	2.3% (15/657)	3.1% (10/320)	-0.84% [-3.06%, 1.38%]	2.8% (18/653)	4.1% (13/320)	-1.31% [-3.81%, 1.20%]
QMI	0.2% (1/657)	0.0% (0/320)	0.15% [Assump. not met]	0.3% (2/653)	0.3% (1/320)	-0.01% [Assump. not met]
NQMI	2.1% (14/657)	3.1% (10/320)	-0.99% [-3.20%, 1.21%]	2.5% (16/653)	3.8% (12/320)	-1.30% [-3.70%, 1.10%]
Cardiac Death or MI	2.9% (19/657)	3.8% (12/320)	-0.86% [-3.30%, 1.59%]	3.4% (22/653)	4.7% (15/320)	-1.32% [-4.02%, 1.38%]
Stent Thrombosis – Protocol defined	0.6% (4/654)	0.0% (0/319)	0.61% [Assump. not met]	0.8% (5/647)	0.6% (2/317)	0.14% [Assump. not met]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Late (> 30 days)	0.2% (1/653)	0.0% (0/319)	0.15% [Assump. not met]	0.3% (2/646)	0.6% (2/317)	-0.32% [Assump. not met]

Notes:

- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- 9 month and 1 year time frames include follow-up window (270 +14 days and 365 + 28 days) respectively.
- 9 months analysis results include 9 month events identified at the 1 year follow-up.
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.
[2] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[3] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.1.1-3: SPIRIT III 8 Month Angiographic and IVUS Results

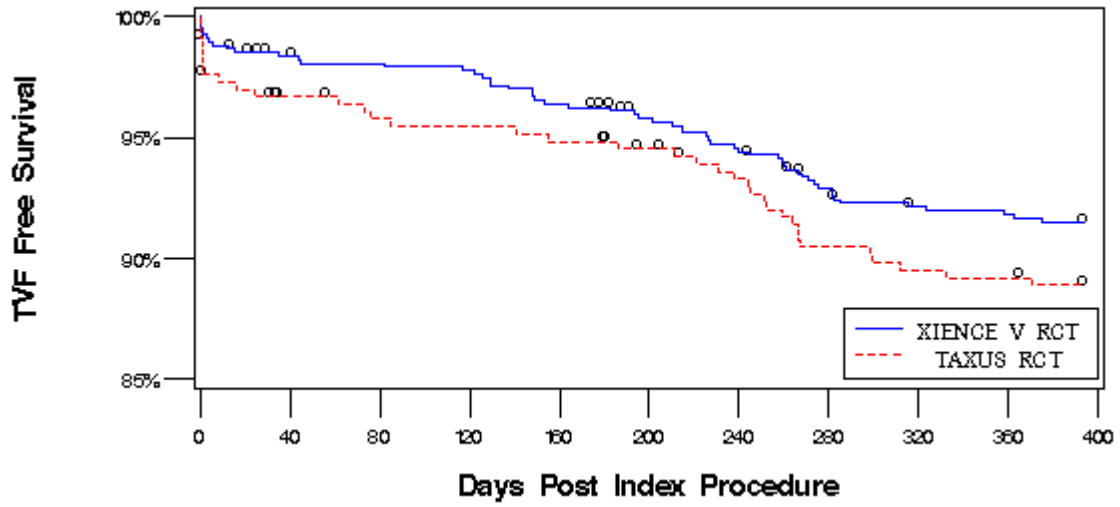
	XIENCE V (N=376) (M_{ANGIO}=427) (M_{IVUS}=181)	TAXUS (N=188) (M_{ANGIO}=220) (M_{IVUS}=93)	Difference [95% CI][1]
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.71 ± 0.43 (425)	2.74 ± 0.40 (220)	-0.03 [-0.10, 0.04]
8 Months	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)	0.11 [-0.01, 0.23]
In-Segment MLD			
Post-Procedure	2.35 ± 0.44 (426)	2.36 ± 0.45 (220)	-0.01 [-0.08, 0.06]
8 Months	2.22 ± 0.53 (344)	2.12 ± 0.60 (158)	0.10 [-0.01, 0.21]
In-Stent %DS			
Post-Procedure	0.32 ± 8.86 (424)	-0.78 ± 10.65 (220)	1.10 [-0.55, 2.74]
8 Months	5.92 ± 16.40 (343)	10.30 ± 21.43 (158)	-4.38 [-8.16, -0.60]
In-Segment %DS			
Post-Procedure	13.89 ± 8.04 (425)	13.92 ± 7.20 (220)	-0.03 [-1.26, 1.19]
8 Months	18.77 ± 14.43 (344)	22.82 ± 16.35 (158)	-4.05 [-7.03, -1.06]
Late Loss			
In-Stent	0.16 ± 0.41 (342)	0.30 ± 0.53 (158)	-0.15 [-0.24, -0.05]
In-Segment	0.14 ± 0.39 (343)	0.26 ± 0.46 (158)	-0.13 [-0.21, -0.04]
Binary Restenosis			
In-Stent	2.3% (8/343)	5.7% (9/158)	-3.36% [-7.32%, 0.59%]
In-Segment	4.7% (16/344)	8.9% (14/158)	-4.21% [-9.17%, 0.75%]
IVUS RESULTS			
Neointimal Volume (mm^3)	10.13 ± 11.46 (101)	20.87 ± 13.51 (41)	-10.74 [-20.92, -0.56]
% Volume Obstruction	6.91 ± 6.35 (98)	11.21 ± 9.86 (39)	-4.30 [-7.72, -0.88]
Incomplete Apposition			
Post Procedure	34.4% (31/90)	25.6% (11/43)	8.86% [-7.46%, 25.19%]
8 month	25.6% (23/90)	16.3% (7/43)	9.28% [-4.97%, 23.52%]
Persistent	24.4% (22/90)	14.0% (6/43)	10.49% [-3.15%, 24.13%]
Late Acquired	1.1% (1/90)	2.3% (1/43)	-1.21% [Assump. not met]

Notes:

- N is the total number of subjects; M_{ANGIO} is the total number of lesions in the protocol required angiographic cohort and M_{IVUS} is the total number of lesions in the protocol required IVUS cohort.
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- 8 month time frame includes follow-up window (240 + 28 days).
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

Figure 9.1.1-1: SPIRIT III: Survival Free of Target Vessel Failure through 1 Year



TVF	Event Free	Event Rate	P-value[1]
XIENCE V	91.5%	8.5%	0.18
TAXUS	88.9%	11.1%	

Note:
– Time Frame includes follow-up window (365 + 28 days).
[1]P-value based on log rank and not adjusted for multiple comparisons

Table 9.1.1-4: SPIRIT III RCT ARC defined Definite+Probable Stent Thrombosis Through 1 Year

	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 1 year)	1.1% (7/648)	0.6% (2/317)	0.45% [Assump. not met]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.4% (3/667)	0.0% (0/330)	0.45% [Assump. not met]
Late (> 30 days)	0.5% (3/647)	0.6% (2/317)	-0.17% [Assump. not met]

Notes:
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Time Frame includes follow-up window (365 + 28 days).
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.1.2 SPIRIT III US 4.0 mm Arm

Primary Objective: The objective of the SPIRIT III 4.0 mm arm was to demonstrate the non-inferiority in in-segment late loss at 240 days compared to the TAXUS arm of the SPIRIT III RCT.

Design: The SPIRIT III 4.0 mm study was a prospective, single-arm, multi-center clinical trial in the United States evaluating the 4.0 mm diameter XIENCE V stent. Sixty-nine (69) subjects were enrolled in the SPIRIT III 4.0 mm study arm.

All subjects had clinical follow-up at 30, 180, 240, and 270 days, and annually from 1 to 5 years. In addition, all subjects had angiographic follow-up at 240 days. IVUS was performed for subjects who received a bailout stent at baseline and 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

Demographics: The mean age in the SPIRIT III 4.0 arm was 61.9 years with 72.5% (50/69) male, 21.7% (15/69) had prior cardiac interventions, and 30.4% (21/69) had a history of diabetes.

Results: The results are presented in Table 9.1.2-1 (Primary endpoints), Table 9.1.2-2 (Clinical Results), Table 9.1.2-3 (Angiographic Results), and Table 9.1.2-4 (ARC-Defined Stent Thrombosis). These analyses were performed on the intent to treat population.

The primary endpoint of in-segment late loss at 240 days was met with measurements of 0.17 ± 0.38 mm (49) for the XIENCE V 4.0 mm arm and 0.28 ± 0.48 mm (134) for the TAXUS arm from the SPIRIT III RCT ($p < 0.0001$ for non-inferiority).

Table 9.1.2-1: SPIRIT III 4.0 mm Primary Endpoints Results

Measurements	XIENCE V (M=69)	TAXUS (M=188)	Difference [95% CI]	Non-Inferiority P-Value
8 Month Late Loss, In-segment (mm)	0.17 ± 0.38 (49)	0.28 ± 0.48 (134)	-0.11 [-0.24, 0.03][1]	<0.0001[2]

Notes:
- M is the total number of analysis lesions.
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Time Frame includes follow-up window (240 + 28 days).

[1] By normal approximation.
[2] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.038 significance level.

Table 9.1.2-2: SPIRIT III 4.0 mm Clinical Results

	OUTCOMES AT 9 MONTHS XIENCE V (N=69)	OUTCOMES AT 1 YEAR (latest available follow-up) XIENCE V (N=69)
COMPOSITE EFFICACY & SAFETY		
TVF[1]	5.9% (4/68)	5.9% (4/68)
MACE[2]	5.9% (4/68)	5.9% (4/68)
EFFICACY		
Ischemia-Driven TLR	1.5% (1/68)	1.5% (1/68)
TLR, CABG	0.0% (0/68)	0.0% (0/68)
TLR, PCI	1.5% (1/68)	1.5% (1/68)
Ischemia-Driven non-TLR TVR	0.0% (0/68)	0.0% (0/68)
non-TLR TVR, CABG	0.0% (0/68)	0.0% (0/68)
non-TLR TVR, PCI	0.0% (0/68)	0.0% (0/68)
SAFETY		
All Death	1.5% (1/68)	1.5% (1/68)
Cardiac Death	1.5% (1/68)	1.5% (1/68)
Non-Cardiac Death	0.0% (0/68)	0.0% (0/68)
MI	4.4% (3/68)	4.4% (3/68)
QMI	0.0% (0/68)	0.0% (0/68)
NQMI	4.4% (3/68)	4.4% (3/68)
Cardiac Death or MI	5.9% (4/68)	5.9% (4/68)
Stent Thrombosis – Protocol defined	1.5% (1/67)	1.5% (1/67)
Acute (< 1 day)	1.4% (1/69)	1.4% (1/69)
Subacute (1 – 30 days)	0.0% (0/69)	0.0% (0/69)
Late (> 30 days)	0.0% (0/67)	0.0% (0/67)

Notes:

- 9 months and 1 year time frames include follow-up window (270 +14 days and 365 + 28 days) respectively. 9 month analysis includes 9 month events identified at the 1 year follow-up.

[1] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

[2] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.1.2-3: SPIRIT III 4.0 mm 8 Month Angiographic Results

	XIENCE V (N=69) (M=69)
ANGIOGRAPHIC RESULTS	
In-Stent MLD	
Post-Procedure	3.46 ± 0.38 (69)
8 Months	3.36 ± 0.46 (49)
In-Segment MLD	
Post-Procedure	3.07 ± 0.43 (69)
8 Months	2.91 ± 0.51 (49)
In-Stent %DS	
Post-Procedure	2.12 ± 10.27 (69)
8 Months	4.78 ± 13.20 (49)
In-Segment %DS	
Post-Procedure	13.42 ± 8.08 (69)
8 Months	17.92 ± 10.83 (49)
Late Loss	
In-Stent	0.12 ± 0.34 (49)
In-Segment	0.17 ± 0.38 (49)
Binary Restenosis	
In-Stent	0.0% (0/49)
In-Segment	2.0% (1/49)

Notes:
- N is the total number of subjects; M is the total number of lesions at baseline.
- 8 month time frame includes follow-up window (240 + 28 days).

Table 9.1.2-4: SPIRIT III 4.0 mm ARC defined Definite+Probable Stent Thrombosis Through 1 Year

	XIENCE V (N=69)
ARC Definite+Probable Stent Thrombosis (0 days – 1 year)	0.0% (0/67)
Acute (< 1 day)	0.0% (0/69)
Subacute (1 – 30 days)	0.0% (0/69)
Late (> 30 days)	0.0% (0/67)

Notes:
- Time Frame includes follow-up window (365 + 28 days).

9.2 SPIRIT II Supportive Clinical Trial

Primary Objective: The objective of the SPIRIT II clinical study was to demonstrate the non-inferiority in in-stent late loss at 180 days of the XIENCE V stent to the TAXUS stent in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel. The SPIRIT II clinical study arm allowed the treatment of *de novo* lesions ≤ 28 mm in length in coronary arteries with a reference vessel diameter (RVD) ≥ 2.5 mm to ≤ 4.25 mm. If non-inferiority of in-stent late loss was demonstrated, it was pre-specified that testing for superiority could be conducted. SPIRIT II was performed outside of the U.S.

Design: The SPIRIT II clinical study was a prospective, active-control, 3:1 (XIENCE V:TAXUS) randomized, single-blind, multi-center non-inferiority evaluation of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 4.25 mm. Given the available Xience V stent lengths of 8, 18 and 28 mm for this trial, in the Xience V arm, treatment of a target lesion > 22 mm and ≤ 28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent. In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage.

Three hundred (300) subjects were enrolled in the study at 28 international sites in Europe, India and New Zealand.

All subjects had clinical follow-up at 30, 180, and 270 days, and annually from 1 to 5 years. All subjects had angiographic follow-up at 180 days with planned additional angiographic and IVUS follow-up at 2 years in a pre-specified subgroup of 152 consecutively enrolled subjects at selected sites.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

A subgroup of 39 subjects were enrolled in a pharmacokinetic (PK) substudy. Venous blood was drawn at regular intervals for PK analysis of total blood everolimus level at 7 pre-determined sites.

Demographics: The mean age was 62.0 years for the XIENCE V arm and 61.9 years for the TAXUS arm. The XIENCE V had 70.9% (158/223) males and the TAXUS arm had 79.2% (61/77) males. The XIENCE V arm had 23.3% (52/223) of subjects with prior cardiac interventions and the TAXUS arm had 22.1% (17/77). The XIENCE V arm had 22.9% (51/223) of subjects with a history of diabetes and the TAXUS arm had 23.7% (18/76). The XIENCE V had 16.6% (37/223) of subjects with a lesion treated in two vessels and TAXUS had 18.2% (14/77). The XIENCE V arm had 10.8% (24/223) of subjects with planned stent overlap. The XIENCE V arm had 18.4% (40/217) of subjects with a history of an MI within two months while the TAXUS arm had 7.8% (6/77) (p=0.0284). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

Results: The results are presented in Table 9.2-1 (Primary endpoint), Table 9.2-2 (Clinical Results), Table 9.2-3 (Angiographic and IVUS Results), and Table 9.2-4 (ARC-Defined Stent Thrombosis). These analyses were based on the intent to treat population.

The primary endpoint of in-stent late loss at 180 days was met with measurements of 0.11 ± 0.27 mm (201) for the XIENCE V arm and 0.36 ± 0.39 mm (73) for the TAXUS arm ($p < 0.0001$ for non-inferiority). In a prespecified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-stent late loss at 180 days ($p < 0.0001$).

Table 9.2-1: SPIRIT II Primary Endpoint Result

Measurements	XIENCE V (N=223) (M=201)	TAXUS (N=77) (M=73)	Difference [95% CI]	Non-Inferiority P-Value	Superiority P-Value
180 Day Late Loss, In-stent (mm)	0.11 ± 0.27 (201)	0.36 ± 0.39 (73)	-0.24 [-0.34, -0.15][1]	<0.0001[2]	<0.0001[3]

Notes:

– N is the number of subjects and M is the total number of analysis lesions.

[1]By normal approximation.

[2]One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.16 mm, to be compared at a 0.0448 significance level.

[3]P-value from two-sided t-test.

Table 9.2-2: SPIRIT II Clinical Results

	OUTCOMES AT 6 MONTHS			OUTCOMES AT 2 YEARS (latest available follow-up)		
	XIENCE V (N=223)	**TAXUS (N=77)**	**Difference [95% CI][1]**	**XIENCE V (N=223)**	**TAXUS (N=77)**	Difference [95% CI][1]
COMPOSITE EFFICACY & SAFETY						
TVF[2]	3.6% (8/222)	6.5% (5/77)	-2.89% [-8.92%, 3.14%]	10.0% (21/211)	12.3% (9/73)	-2.38% [-10.93%, 6.18%]
MACE[3]	2.7% (6/222)	6.5% (5/77)	-3.79% [-9.69%, 2.11%]	6.6% (14/211)	11.0% (8/73)	-4.32% [-12.24%, 3.59%]
EFFICACY						
Ischemia-Driven TLR	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	3.8% (8/211)	6.8% (5/73)	-3.06% [-9.40%, 3.28%]
TLR, CABG	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/211)	0.0% (0/73)	0.00% [Assump. not met]
TLR, PCI	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	3.8% (8/211)	6.8% (5/73)	-3.06% [-9.40%, 3.28%]
Ischemia-Driven non-TLR TVR	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	3.8% (8/211)	4.1% (3/73)	-0.32% [Assump. not met]
non-TLR TVR, CABG	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.5% (1/211)	0.0% (0/73)	0.47% [Assump. not met]
non-TLR TVR, PCI	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	3.3% (7/211)	4.1% (3/73)	-0.79% [Assump. not met]
SAFETY						
All Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	3.7% (8/218)	6.5% (5/77)	-2.82% [-8.87%, 3.22]
Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	0.5% (1/218)	1.3% (1/77)	-0.84% [Assump. not met]
Non-Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	3.2% (7/218)	5.2% (4/77)	-1.98% [Assump. not met]
MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	2.8% (6/211)	5.5% (4/73)	-2.64% [Assump. not met]
QMI	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/211)	0.0% (0/73)	0.00% [Assump. not met]
NQMI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	2.8% (6/211)	5.5% (4/73)	-2.64% [Assump. not met]
Cardiac Death or MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	3.3% (7/211)	5.5% (4/73)	-2.16% [Assump. not met]
Stent Thrombosis – Protocol defined	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	1.9% (4/211)	1.4% (1/73)	0.53% [Assump. not met]
Acute (< 1 day)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Late (> 30 days)	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	1.9% (4/211)	1.4% (1/73)	0.53% [Assump. not met]

Notes:

- 6 months and 2 year time frames include follow-up window (180 +14 days and 730 + 28 days).
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.
[2] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[3] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.2-3: SPIRIT II 180-Day Angiographic and IVUS Results

	XIENCE V (N=223) (M=260)	TAXUS (N=77) (M=91)	**Difference [95% CI][1]**
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.49 ± 0.40 (260)	2.62 ± 0.45 (91)	-0.13 [-0.24, -0.03]
6 Months	2.38 ± 0.50 (237)	2.27 ± 0.54 (86)	0.10 [-0.03, 0.23]
In-Segment MLD			
Post-Procedure	2.15 ± 0.44 (260)	2.22 ± 0.53 (91)	-0.07 [-0.19, 0.05]
6 Months	2.10 ± 0.51 (237)	2.08 ± 0.54 (86)	0.02 [-0.11, 0.15]
In-Stent %DS			
Post-Procedure	13.01 ± 6.02 (260)	12.66 ± 5.53 (91)	0.35 [-1.01, 1.71]
6 Months	15.70 ± 9.88 (237)	20.89 ± 11.59 (86)	-5.18 [-7.96, -2.41]
In-Segment %DS			
Post-Procedure	22.51 ± 8.98 (260)	23.36 ± 11.20 (91)	-0.86 [-3.43, 1.72]
6 Months	23.61 ± 11.65 (237)	27.05 ± 12.68 (86)	-3.44 [-6.53, -0.35]
Late Loss			
In-Stent	0.12 ± 0.29 (237)	0.37 ± 0.38 (86)	-0.25 [-0.34, -0.16]
In-Segment	0.07 ± 0.33 (237)	0.15 ± 0.38 (86)	-0.08 [-0.17, 0.01]
Binary Restenosis			
In-Stent	1.3% (3/237)	3.5% (3/86)	-2.22% [Assump. not met]
In-Segment	3.4% (8/237)	5.8% (5/86)	-2.44% [-7.89%, 3.02%]
IVUS RESULTS			
Neointimal Volume (mm^3)	3.83 ± 6.55 (99)	14.42 ± 16.03 (40)	-10.60 [-15.87, -5.32]
% Volume Obstruction	2.51 ± 4.68 (99)	7.36 ± 7.05 (40)	-4.85 [-7.27, -2.42]
Incomplete Apposition			
Post Procedure	6.5% (7/108)	5.6% (2/36)	0.93% [Assump. not met]
6 month	2.9% (3/103)	0.0% (0/39)	2.91% [Assump. not met]
Persistent	2.5% (3/120)	0.0% (0/42)	2.50% [Assump. not met]
Late Acquired	0.0% (0/104)	0.0% (0/39)	0.00% [Assump. not met]

Notes:
- N is the total number of subjects; M is the total number of lesions.
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

Table 9.2-4: SPIRIT II ARC defined Definite+Probable Stent Thrombosis Through 2 Years

	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 2 years)	0.9% (2/211)	1.4% (1/73)	-0.42% [Assump. not met]
Acute (< 1 day)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/223)	1.3% (1/77)	-1.30% [Assump. not met]
Late (31 days – 1 year)	0.0% (0/220)	1.3% (1/77)	-1.30% [Assump. not met]
Very Late (1 – 2 years)	0.9% (2/211)	0.0% (0/72)	0.95% [Assump. not met]

Note:
– Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.
[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.3 SPIRIT FIRST Randomized Clinical Trial

Objective: The objective of the SPIRIT FIRST randomized clinical trial was to assess the feasibility and performance of the XIENCE V stent (called VISION-E within the SPIRIT FIRST study) in the treatment of subjects with a single *de novo* native coronary artery lesion with reference vessel diameter (RVD) of 3.0 mm and lesion length ≤ 12 mm. This study compared the XIENCE V stent to a matched uncoated metallic stent control (MULTI-LINK VISION).

Design: SPIRIT FIRST was a single-blind multi-center randomized controlled trial to assess the safety and performance of everolimus eluting from a durable polymer on a cobalt chromium stent (XIENCE V stent). Sixty (60) subjects were enrolled in the study.

All subjects had clinical follow-up at 30, 180, and 270 days, and annually from 1 to 5 years. All subjects had angiography and IVUS at baseline and at 180 days and 1 year follow-up.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 3 months and aspirin daily to be taken throughout the length of the trial (1 year).

Demographics: The mean age was 64.2 years for the XIENCE V arm and 61.4 years for the VISION arm. The XIENCE V had 70.4% (19/27) males and the VISION arm had 75.9% (22/29) males. The XIENCE V arm had 18.5% (5/27) subjects with prior cardiac interventions and the VISION arm had to 6.9% (2/29). The XIENCE V arm had 11.1% (3/27) subjects with a history of diabetes and the VISION arm had 10.3% (3/29). XIENCE V arm had 70.4% (19/27) of subjects with hypertension requiring medication while the VISION arm had 41.4% (12/29) (p=0.035). The remaining subject baseline clinical features were also well-matched between the XIENCE V arm and the VISION arm.

Results: The results are presented in Table 9.3-1 (Primary endpoint), Table 9.3-2 (Clinical Results), Table 9.3-3 (Angiographic and IVUS Results), and Table 9.3-4 (ARC-Defined Stent Thrombosis). These analyses were based on the per protocol evaluable population.

The primary superiority endpoint of in-stent late loss at 180 days was met with measurements of 0.10 ± 0.23 mm (23) for the XIENCE V arm and 0.85 ± 0.36 mm (27) for the MULTI-LINK VISION arm (p < 0.0001).

Table 9.3-1: SPIRIT FIRST Primary Endpoint Result

Measurements	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][1]	Superiority P-value [2]
180 Days Late Loss, In-stent (mm)	0.10± 0.23 (23)	0.85± 0.36 (27)	-0.76 [-0.93, -0.59] [1]	< 0.0001

Note: N is the number of subjects.
[1]By normal approximation
[2]One-tailed p-value by t-test, to be compared to a 5% significance level

Table 9.3-2: SPIRIT FIRST Clinical Results

	OUTCOMES AT 6 MONTHS[1]			OUTCOMES AT 3 YEARS[1] (latest available follow-up)		
	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][2]	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][2]
COMPOSITE EFFICACY & SAFETY						
TVF[3]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]]	15.4% (4/26)	32.1% (9/28)	-16.76% [Assump. not met]
MACE[4]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]	15.4% (4/26)	25.0% (7/28)	-9.62% [Assump. not met]
EFFICACY						
Ischemia-Driven TLR	3.8% (1/26)	21.4% (6/28)	-17.58% [Assump. not met]	7.7% (2/26)	25.0% (7/28)	-17.31% [Assump. not met]
TLR, CABG	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]
TLR, PCI	3.8% (1/26)	17.9% (5/28)	-14.01% [Assump. not met]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]
Ischemia-Driven non-TLR TVR	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	10.7% (3/28)	-10.71% [Assump. not met]
non-TLR TVR, CABG	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]
non-TLR TVR, PCI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	7.1% (2/28)	-7.14% [Assump. not met]
SAFETY						
All Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Non-Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	7.7% (2/26)	0.0% (0/28)	7.69% [Assump. not met]
QMI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]
NQMI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]
Cardiac Death or MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	7.7% (2/26)	0.0% (0/28)	7.69% [Assump. not met]
Stent Thrombosis – Protocol defined	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]
Late (> 30 days)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]

Note:

¯ Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] 6 month and 3 year time frames include follow-up window (180 +14 days and 1095 + 28 days) respectively.

[2] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

[3] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

[4] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.3-3: SPIRIT FIRST 180-Day Angiographic and IVUS Results

	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][1]
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.34± 0.26 (27)	2.43± 0.30 (29)	-0.09 [-0.24, 0.06]
6 Months	2.28± 0.33 (23)	1.58± 0.41 (27)	0.70 [0.49,0.91]
In-Segment MLD			
Post-Procedure	2.07± 0.37 (27)	2.15± 0.37 (29)	-0.08 [-0.28, 0.12,]
6 Months	2.04 ± 0.40 (23)	1.54± 0.41 (27)	0.50 [0.27, 0.73]
In-Stent %DS			
Post-Procedure	12.34 ± 4.02 (27)	14.85 ± 4.76 (29)	-2.51 [-4.87, -0.16]
6 Months	15.57 ± 7.64 (23)	38.61 ± 14.25 (27)	-23.05 [-29.45, -16.64]
In-Segment %DS			
Post-Procedure	20.82 ± 7.65 (27)	23.14 ± 8.03% (29)	-2.32 [-6.52, 1.88]
6 Months	21.89 ± 11.15 (23)	40.78 ± 13.67 (27)	-18.89 [-25.95,-11.83]
Late Loss			
In-Stent	0.10 ± 0.23 (23)	0.85 ± 0.36 (27)	-0.76 [-0.93, -0.59]
In-Segment	0.09 ± 0.20 (23)	0.61 ± 0.37 (27)	-0.53 [-0.69, -0.36]
Binary Restenosis			
In-Stent	0.0% (0/23)	25.9% (7/27)	-25.93% [Assump. not met]
In-Segment	4.3% (1/23)	33.3% (9/27)	-28.99% [Assump. not met]
IVUS RESULTS			
Neointimal Volume (mm^3)	10.29± 13.32 (21)	38.29± 19.08 (24)	-28.00 [-37.82, -18.19]
% Volume Obstruction	7.95± 10.44 (21)	28.11± 13.98 (24)	-20.16 [-27.53, -12.79]
Incomplete Apposition			
Post Procedure	0.0% (0/ 27)	10.7% (3/ 28)	-10.71% [Assump. not met]
6 month	0.0% (0/ 21)	0.0% (0/ 22)	0.00% [Assump. not met]
Persistent	0.0% (0/ 27)	0.0% (0/ 28)	0.00% [Assump. not met]
Late Acquired	0.0% (0/ 21)	0.0% (0/ 22)	0.00% [Assump. not met]

Note:

⁻ Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1]Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

Table 9.3-4: SPIRIT FIRST ARC defined Definite+Probable Stent Thrombosis Through 3 Years

	XIENCE V (N=27)	VISION (N=29)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 3 years)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Late (31 days – 1 year)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Very Late (1 – 3 years)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]

Note:

- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.4 SPIRIT II AND SPIRIT III POOLED ANALYSIS

In order to better estimate the incidence of low frequency events or outcomes in various specific subject subgroups, a subject-level pooled analysis was conducted of both randomized trials comparing the XIENCE V stent versus the TAXUS stent. Data from the SPIRIT II and SPIRIT III clinical trials were pooled to compare the XIENCE V stent to the TAXUS control stent in 1302 subjects out to 1 year (393 days) of follow-up. These two studies have subjects with similar baseline and angiographic characteristics and the key elements of study design including inclusion and exclusion criteria and endpoint definitions are comparable. The subject level data were included until the latest available time point of 1 year for each trial. Table 9.4-1 shows the subject disposition over time for the SPIRIT II and III RCT. The percentage of the total number of subjects that were enrolled in the studies and completed their 1 year follow-up was 96.5%.

Table 9.4-1: Subject Disposition Table (N=1302; SPIRIT II and SPIRIT III RCT)

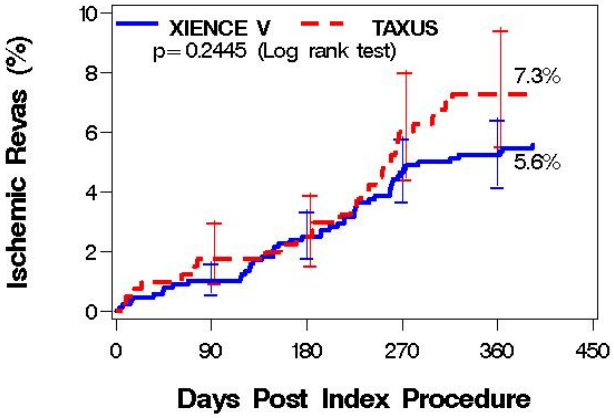
	30-Day Follow-up		9-Month Follow-up		1-Year Follow-up	
	XIENCE V (890)		XIENCE V (873)		XIENCE V (866)	
	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III
Subjects	223	667	220	653	220	646
	TAXUS (407)		TAXUS (395)		TAXUS (392)	
	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III
Subjects	77	330	76	319	76	316

It is acknowledged that these retrospective pooled analyses are exploratory and hypothesis-generating. Definitive proof of the presence or absence of any differences between such sub-groups requires prospectively powered assessment in dedicated clinical trials. The pooled analysis from SPIRIT II and SPIRIT III trials includes subjects from single-blind trials with similar inclusion and exclusion criteria in 1,302 subjects with 1,506 lesions.

As shown in Figure 9.4-1, at one year, the analyses of pooled trials suggest a reduction in the rates of TVR and TLR for the XIENCE V stent compared to the TAXUS stent through one year. All CI bars represent a 1.5 standard error.

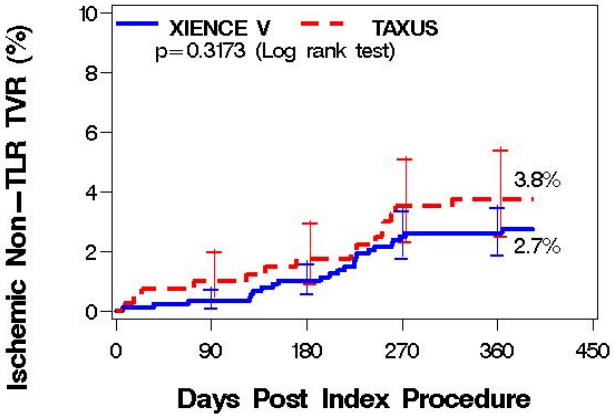
Figure 9.4-1: Kaplan Meier Hazard Curves for Time to First TVR or TLR Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

TVR (Includes TLR and Non-TLR TVR)



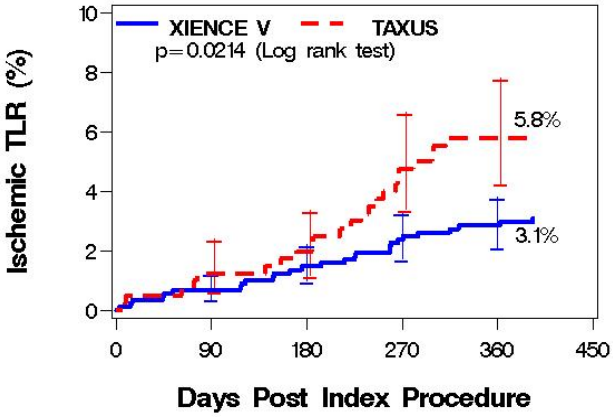
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Non-TLR TVR



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

TLR

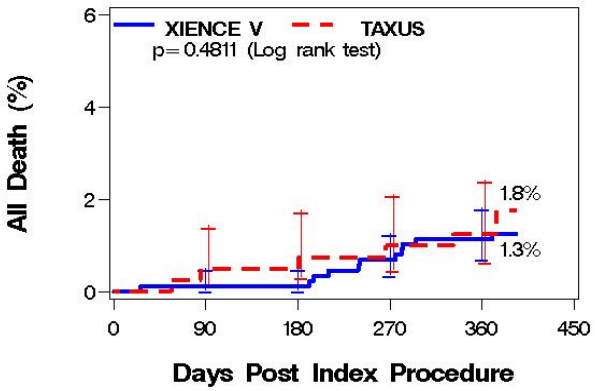


Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of all death, cardiac death, and non-cardiac death through 1 year are shown in Figure 9.4-2.

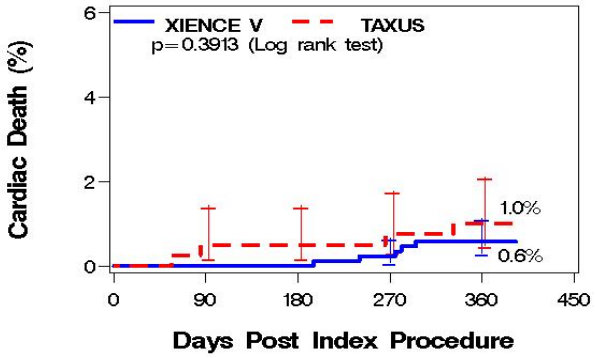
Figure 9.4-2: Kaplan Meier Hazard Curves for Time to Death through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

All Death



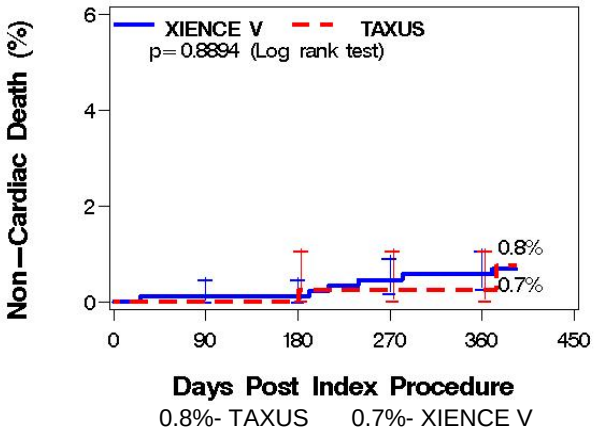
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Cardiac-Death



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

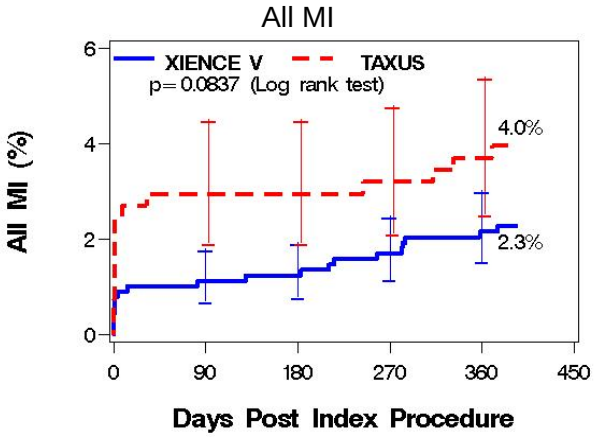
Non-Cardiac Death



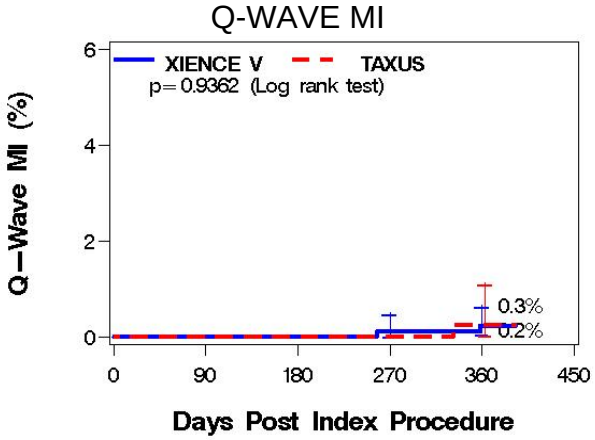
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of MIs through 1 year are shown in Figure 9.4-3.

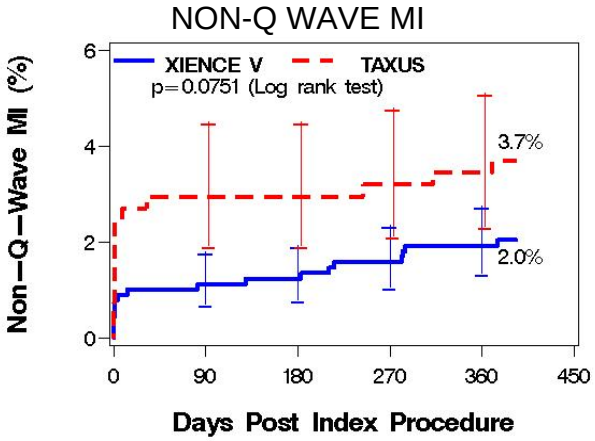
Figure 9.4-3: Kaplan Meier Hazard Curves for Time to First MI Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

9.4.1 Stent Thrombosis in SPIRIT II and SPIRIT III Pooled Analysis

The results for the pooled analysis rates of stent thrombosis at one year are shown below in Figure 9.4.1-1. Rates were low for both treatments in this pooled analysis and consistent with the published literature[10]. The rates of stent thrombosis were evaluated based on the SPIRIT II and III protocol defined definition and the ARC definition for definite + probable thrombosis (see definitions above in Section 8.2). These data are presented in table 9.4.1-1.

Table 9.4.1-1 Pooled Results for Stent Thrombosis through 1 year (SPIRIT II and SPIRIT III RCT)

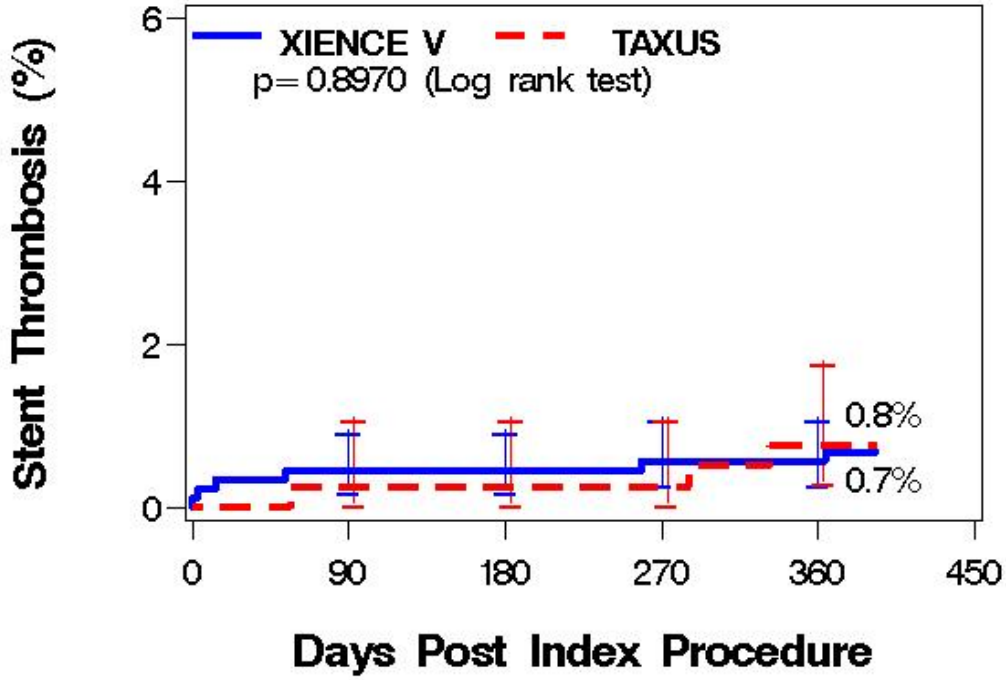
	XIENCE V (N=892)	95% CI[1]	TAXUS (N=410)	95% CI[1]
0 - 30 days				
Protocol	0.3% (3/890)	[0.07%, 0.98%]	0.0% (0/407)	[0.00%, 0.90%]
ARC (definite + probable)	0.4% (4/890)	[0.12%, 1.15%]	0.2% (1/407)	[0.01%, 1.36%]
31 days – 1 year				
Protocol	0.3% (3/866)	[0.07%, 1.01%]	0.8% (3/394)	[0.16%, 2.21%]
ARC (definite + probable)	0.3% (3/867)	[0.07%, 1.01%]	0.8% (3/394)	[0.16%, 2.21%]
0 – 1 year				
Protocol	0.7% (6/867)	[0.25%, 1.50%]	0.8% (3/394)	[0.16%, 2.21%]
ARC (definite + probable)	0.8% (7/868)	[0.32%, 1.65%]	0.8% (3/394)	[0.16%, 2.21%]

Note: timeframe for 1 year includes the follow-up window (365 + 28 days).
[1] By Clopper-Pearson Exact Confidence Interval

[10] Ellis SG CA, Grube E, Popma J, Koglin J, Dawkins KD, Stone GW. Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed for up to 3 years. *J Am Coll Cardiol.* 2007;49:1043-1051.

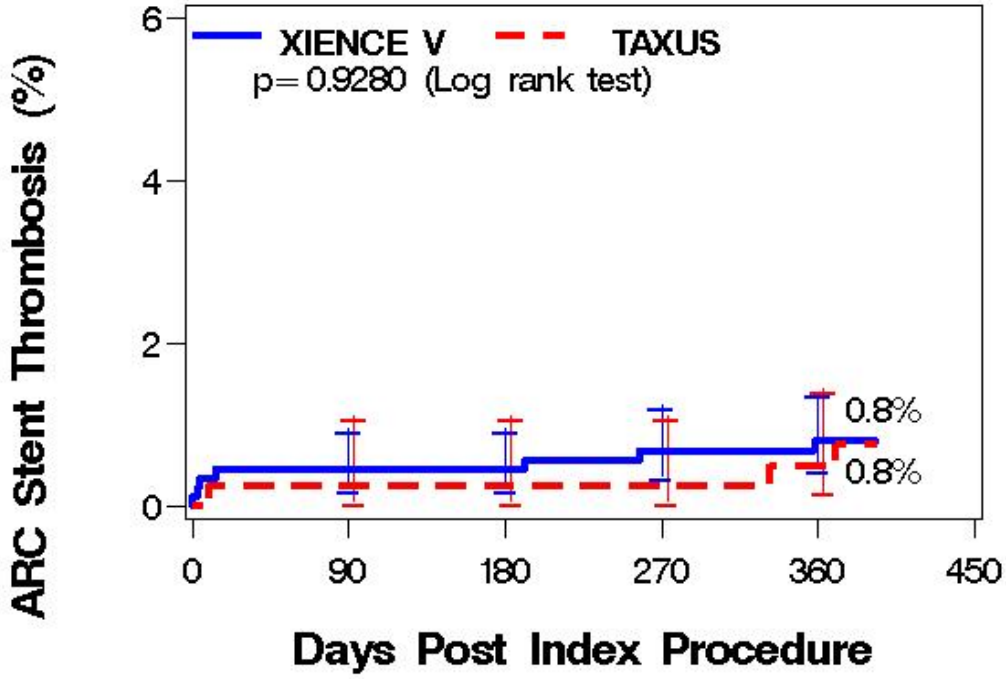
Figure 9.4.1-1: Kaplan Meier Hazard Curves for Time to First Stent Thrombosis Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

Protocol Defined Stent Thrombosis



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

ARC Defined Stent Thrombosis (Definite + Probable)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

9.4.2 Diabetics in SPIRIT II and SPIRIT III Pooled Analysis

Diabetic subjects comprise an important subject subgroup that is at increased risk for cardiovascular morbidity and mortality. Although diabetic subjects were included in the SPIRIT family of trials, there were no pre-specified hypotheses or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in diabetic individuals.

Table 9.4.2-1 shows the clinical outcomes through 1 year in subjects pooled from SPRIT II and III. The randomization was stratified by history of diabetes to assure a balance between the XIENCE V and TAXUS treatment arms. In XIENCE V patients, there were numerically higher event rates in diabetics compared with non-diabetics. The event rates for TAXUS in diabetics were lower than the event rates for TAXUS non-diabetics. Given the relatively small sample size of the diabetic population and potential for confounding variables, no conclusions can be drawn from these post-hoc analyses.

Table 9.4.2-1: Clinical Results in Diabetics and Non-Diabetics through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population)

	Non-Diabetics XIENCE V (N=643)	Non-Diabetics TAXUS (N=296)	All Diabetics XIENCE V (N=249)	All Diabetics TAXUS (N=110)
TLR	2.5% (16/629)	7.6% (22/290)	4.5% (11/244)	1.0% (1/104)
TVR(CABG/PCI), non TL	2.5% (16/629)	4.1% (12/290)	3.3% (8/244)	2.9% (3/104)
All Death	1.0% (6/631)	2.4% (7/291)	2.0% (5/246)	0.0% (0/104)
Cardiac Death	0.3% (2/631)	1.4% (4/291)	1.2% (3/246)	0.0% (0/104)
Non-Cardiac Death	0.6%(4/631)	1.0%(3/291)	0.8%(2/246)	0.0% (0/104)
MI	1.4% (9/629)	4.5% (13/290)	4.5% (11/244)	2.9% (3/104)
Cardiac Death or MI	1.7% (11/629)	5.2% (15/290)	5.3% (13/244)	2.9% (3/104)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.0% (3/287)	1.3% (3/240)	0.0% (0/104)
ARC definite + probable	0.3% (2/627)	0.7% (2/287)	2.1% (5/241)	1.0% (1/104)

Table 9.4.2-2: Clinical Results in Diabetics through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population – XIENCE V Subjects)

	Non-Diabetics (N=643)	All Diabetics (N=249)	Insulin-Dependent Diabetics (N=63)	Non-Insulin-Dependent Diabetics (N=186)
TLR	2.5% (16/629)	4.5% (11/244)	6.5% (4/62)	3.8% (7/182)
TVR(CABG/PCI), non TL	2.5% (16/629)	3.3% (8/244)	1.6% (1/62)	3.8% (7/182)
All Death	1.0% (6/631)	2.0% (5/246)	3.2% (2/63)	1.6% (3/183)
Cardiac Death	0.3% (2/631)	1.2% (3/246)	1.6% (1/63)	1.1% (2/183)
Non-Cardiac Death	0.6% (4/631)	0.8%(2/246)	1.6% (1/63)	0.5% (1/183)
MI	1.4% (9/629)	4.5% (11/244)	9.7% (6/62)	2.7% (5/182)
Cardiac Death or MI	1.7% (11/629)	5.3% (13/244)	9.7% (6/62)	3.8% (7/182)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.3% (3/240)	1.6% (1/61)	1.1% (2/179)
ARC definite + probable	0.3% (2/627)	2.1% (5/241)	1.6% (1/61)	2.2% (4/180)

9.4.3 Dual Vessel treatment in SPIRIT II and SPIRIT III Pooled Analysis

Subjects requiring treatment in more than one vessel comprise a subgroup that is at increased risk for cardiovascular events compared with single vessel disease patients. Although subjects requiring both single and dual vessel treatment were included in the SPIRIT family of trials,

there were no pre-specified hypothesis or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in dual vessel individuals.

Table 9.4.3-1 shows the clinical outcomes through 1 year in subjects pooled from SPRIT II and III. The randomization was stratified by the number of vessels treated to assure a balance between the XIENCE V and TAXUS treatment arms. Numerically lower event rates were observed for XIENCE V and TAXUS in single compared to dual vessel treatment. However, given the small sample size for dual vessel treatment, no conclusions can be drawn from this post-hoc analysis.

Table 9.4.3-1: Clinical Results in Single and Dual Vessel Treatment through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population)

	Single Vessel XIENCE V (N=752)	Single Vessel TAXUS (N=344)	Dual Vessel XIENCE V (N=140)	Dual Vessel TAXUS (N=65)
TLR	2.9% (21/735)	4.5% (15/333)	4.3% (6/138)	12.5% (8/64)
TVR(CABG/PCI), non TL	2.3% (17/735)	2.1% (7/333)	5.1% (7/138)	12.5% (8/64)
All Death	1.5% (11/739)	1.2% (4/333)	0.0% (0/138)	4.6% (3/65)
Cardiac Death	0.7% (5/739)	0.6% (2/333)	0.0% (0/138)	3.1% (2/65)
Non-Cardiac Death	0.8% (6/739)	0.6% (2/333)	0.0% (0/138)	1.5% (1/65)
MI	1.9% (14/735)	3.0% (10/333)	4.3% (6/138)	9.4% (6/64)
Cardiac Death or MI	2.4% (18/735)	3.3% (11/333)	4.3% (6/138)	10.9% (7/64)
Stent Thrombosis				
Protocol defined	0.3% (2/729)	0.6% (2/332)	2.9% (4/138)	1.6% (1/62)
ARC definite + probable (TLR not censored)	0.5% (4/730)	0.6% (2/332)	2.2% (3/138)	1.6% (1/62)

10.0 INDIVIDUALIZATION OF TREATMENT

The risks and benefits should be considered for each patient before using the XIENCE V stent. Patient selection factors to be assessed should include a judgment regarding risk of long-term antiplatelet therapy. Stenting is generally avoided in those patients at a heightened risk of bleeding (e.g., patients with recently active gastritis or peptic ulcer disease) in which anticoagulation therapy would be contraindicated.

Antiplatelet drugs should be used in combination with the XIENCE V stent. Physicians should use information from the SPIRIT Clinical trials, coupled with current drug eluting stent (DES) literature and the specific needs of individual patients to determine the specific antiplatelet/anticoagulation regimen to be used for their patients in general practice. See also 5.2 – Precautions, Pre- and Post-Procedure Antiplatelet Regimen, Section 5.6 – Precautions, Use in Special Populations and Section 5.7 – Precautions, Lesion/Vessel Characteristics.

Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

11.0 PATIENT COUNSELING AND PATIENT INFORMATION

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with stent placement.
- Discuss the risks associated with an everolimus-eluting stent.
- Discuss the risks of early discontinuation of the antiplatelet therapy.
- Discuss the risks of late stent thrombosis with DES use in higher risk patient subgroups.
- Discuss the risk/benefit issues for this particular patient.
- Discuss alteration to current life-style immediately following the procedure and over the long term.

The following patient materials are available for this product:

- A Patient Information Guide which includes information on coronary artery disease, the implant procedure and the XIENCE V Everolimus Eluting Coronary Stent System (provided to physician, on-line at www.XIENCEV.com/PatientGuide, or by calling customer service 1-800-227-9902).
- A Stent Implant Card that includes both patient information and stent implant information (provided in package)

12.0 HOW SUPPLIED

Sterile: This device is sterilized with ethylene oxide gas, non-pyrogenic. It is intended for single use only. Do not resterilize. Do not use if the package is opened or damaged.

Contents: One (1) XIENCE V Everolimus Eluting Coronary Stent System, one (1) Flushing tool, (for the XIENCE V EECSS Rapid Exchange (RX) Stent System), one (1) Stent Implant Card, one (1) Patient Information Guide.

Storage: Store in a dry, dark, cool place. Protect from light. Do not remove from carton until ready for use. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

13.0 OPERATOR'S INSTRUCTIONS

13.1 Inspection Prior to Use

- Carefully inspect the sterile package before opening and check for damage to the sterile barrier. Do not use if the integrity of the sterile package has been compromised.
- Do not use after the "Use By" date.
- Tear open the foil pouch and remove the inner pouch. **Note: the outside of the inner pouch is NOT sterile.** Open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
- Prior to using the XIENCE V Everolimus Eluting Coronary Stent System, carefully remove the system from the package and inspect for bends, kinks, and other damage. Verify that the stent does not extend beyond the radiopaque balloon markers. Do not

use if any defects are noted. However, **do not manipulate, touch, or handle the stent** with your fingers, which may cause coating damage, contamination or stent dislodgement from the delivery balloon.

Note: At any time during use of the XIENCE V Rapid Exchange (RX) EECSS, if the stainless steel proximal shaft has been bent or kinked, do not continue to use the catheter.

13.2 Materials Required

- Appropriate guiding catheter(s). See Table 1-1, XIENCE V Stent System Product Description
- 2 – 3 syringes (10 – 20 ml)
- 1,000 u/500 ml Heparinized Normal Saline (HepNS)
- 0.014 inch (0.36 mm) x 175 cm (minimum length) guide wire
- Rotating hemostatic valve with appropriate minimum inner diameter [0.096 inch (2.44 mm)]
- 60% contrast diluted 1:1 with heparinized normal saline
- Inflation device
- Pre-deployment dilatation catheter
- Three-way stopcock
- Torque device
- Guide wire introducer
- Appropriate arterial sheath
- Appropriate anticoagulation and antiplatelet drugs

13.3 Preparation

13.3.1 Packaging Removal

Note: The foil pouch is not a sterile barrier. The inner header bag (pouch) within the foil pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.

1. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a Rapid Exchange (RX) system, do not bend or kink the hypotube during removal.

2. Remove the product mandrel and protective stent sheath by grasping the catheter just proximal to the stent (at the proximal balloon bond site), and with the other hand, grasp the stent protector and gently remove distally. If unusual resistance is felt during product mandrel and stent sheath removal, do not use this product and replace with another. Follow product returns procedure for the unused device.

13.3.2 Guide Wire Lumen Flush

1. Over the Wire (OTW) only: Flush the guide wire lumen with HepNS until fluid exits the distal end of the delivery system.

2. Rapid Exchange (RX) only: Flush the guide wire lumen with HepNS using the flushing tool supplied with the product. Insert the flushing tool into the tip of the catheter and flush until fluid exits the guide wire exit notch.

Note: Avoid manipulation of the stent while flushing the guide wire lumen, as this may disrupt the placement of the stent on the balloon.

13.3.3 Delivery System Preparation

1. Prepare an inflation device/syringe with diluted contrast medium.

2. Attach an inflation device/syringe to the stopcock; attach it to the inflation port of the product. Do not bend the product hypotube when connecting to the inflation device/syringe.

3. With the tip down, orient the delivery system vertically.

4. Open the stopcock to delivery system; pull negative for 30 seconds; release to neutral for contrast fill.

5. Close the stopcock to the delivery system; purge the inflation device/syringe of all air.

6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.

7. If a syringe was used, attach a prepared inflation device to stopcock.

8. Open the stopcock to the delivery system.

9. Leave on neutral

Note: If air is seen in the shaft, repeat *Delivery System Preparation* steps 3 through 5 to prevent uneven stent expansion.

13.4 Delivery Procedure

1. Prepare the vascular access site according to standard practice.

2. **Pre-dilate the lesion with a PTCA catheter of appropriate length and diameter for the vessel/lesion to be treated.** Limit the longitudinal length of pre-dilatation by the PTCA balloon to avoid creating a region of vessel injury that is outside the boundaries of the XIENCE V Stent.

Note: The labeled stent diameter refers to expanded stent inner diameter.

3. Maintain neutral pressure on the inflation device attached to the delivery system. Open the rotating hemostatic valve as wide as possible.

4. Backload the delivery system onto the proximal portion of the guide wire while maintaining guide wire position across the target lesion.

5. Carefully advance the delivery system into the guiding catheter and over the guide wire to the target lesion. When using a Rapid Exchange (RX) system be sure to keep the hypotube straight. Ensure guiding catheter stability before advancing the stent system into the coronary artery.

Note: If unusual resistance is felt before the stent exits the guiding catheter, do not force passage. Resistance may indicate a problem and the use of excessive force may result in stent damage or dislodgement. Maintain guide wire placement across the lesion and remove the delivery system and guiding catheter as a single unit.

6. Advance the delivery system over the guide wire to the target lesion under direct fluoroscopic visualization. Utilize the radiopaque balloon markers to position the stent across the lesion. Perform angiography to confirm stent position. If the position of the stent is not optimal, it should be carefully repositioned or removed (see Section 5.14 – Precautions, Delivery System Removal). The balloon markers indicate both the stent edges and the balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion.

Note: Should **any resistance** be felt **at any time** during either lesion access or removal of the delivery system post-stent implantation, **remove the entire system as a single unit.** See Section 5.14 – Precautions, Delivery System Removal for specific delivery system removal instructions.

7. Tighten the rotating hemostatic valve. The stent is now ready to be deployed.

13.5 Deployment Procedure

CAUTION: Refer to Table 14-1: Typical XIENCE V Stent Compliance for *in vitro* stent inner diameter, nominal pressure, and RBP.

1. Prior to deployment, reconfirm the correct position of the stent relative to the target lesion using the radiopaque balloon markers.

2. Deploy the stent slowly by pressurizing the delivery system in 2 atm increments, every 5 seconds, until stent is completely expanded. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter ratio of about 1.1 times the reference vessel diameter (see Table 14-1). Maintain pressure for 30 seconds. If necessary, the delivery system can be repressurized or further pressurized to assure complete apposition of the stent to the artery wall. **Do not exceed the labeled rated burst pressure (RBP) of 16 atm (1.62 MPa).**

3. Fully cover the entire lesion and balloon treated area (including dissections) with the XIENCE V stent, allowing for adequate stent coverage into healthy tissue proximal and distal to the lesion.

4. Deflate the balloon by pulling negative on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to guiding catheter position.

5. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).

6. If the deployed stent size is still inadequate with respect to reference vessel diameter, a larger balloon may be used to further expand the stent. If the initial angiographic appearance is sub-optimal, the stent may be further expanded using a low profile, high pressure, non-compliant balloon dilatation catheter. If this is required, the stented segment should be carefully recrossed with a prolapsed guide wire to avoid disrupting the stent geometry. Deployed stents should not be left under-dilated.

CAUTION: Do not dilate the stent beyond the following limits.

Nominal Stent Diameter	Dilatation Limit
2.5 mm to 3.0 mm	**3.5 mm**
3.5 mm to 4.0 mm	**4.5 mm**

7. If more than one XIENCE V stent is needed to cover the lesion and balloon

treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between stents the balloon marker bands of the second XIENCE V stent should be positioned inside the deployed stent prior to expansion.

8. Reconfirm stent position and angiographic results. Repeat inflations until optimal stent deployment is achieved.

13.6 Removal Procedure

1. Deflate the balloon by pulling negative pressure on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to the guiding catheter position.

2. Fully open the rotating hemostatic valve.

3. While maintaining the guide wire position and negative pressure on the inflation device, withdraw the delivery system.

Note: Should **any resistance** be felt **at any time** during either lesion access or removal of the delivery system post-stent implantation, the entire system should be **removed as a single unit.** See Section 5.14 – Precautions, Delivery System Removal for specific delivery system removal instructions.

4. Tighten the rotating hemostatic valve.

5. Repeat angiography to assess the stented area. If post-dilatation is necessary, ensure that the final stent diameter matches the reference vessel diameter. **Assure that the stent is not under-dilated.**

13.7 Post-Deployment Dilatation of Stent Segments

1. All efforts should be taken to assure that the stent is not underdilated. If the deployed stent size is still inadequate with respect to the vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. The stent may be further expanded using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guide wire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

CAUTION: Do not dilate the stent beyond the following limits.

Nominal Stent Diameter	Dilatation Limit
2.5 mm to 3.0 mm	**3.5 mm**
3.5 mm to 4.0 mm	**4.5 mm**

14.0 *IN VITRO* COMPLIANCE INFORMATION

Table 14-1: Typical XIENCE V Stent Compliance
Nominal pressure for each diameter indicated by bold font.

Pressure		Stent ID (mm) by System Size				
(atm)	(MPa)	2.5 mm	2.75 mm	3.0 mm	3.5 mm	4.0 mm
8	0.81	**2.46**	**2.74**	2.90	3.46	3.86
9	0.91	2.52	2.81	**2.97**	**3.55**	**3.95**
10	1.01	2.58	2.87	3.04	3.63	4.03
11	1.11	2.63	2.92	3.10	3.69	4.10
12	1.22	2.68	2.97	3.15	3.75	4.17
13	1.32	2.72	3.01	3.19	3.80	4.23
14	1.42	2.75	3.05	3.23	3.84	4.28
15	1.52	2.78	3.08	3.26	3.89	4.33
16 (RBP)*	1.62	2.81	3.11	3.30	3.93	4.37
17	1.72	2.84	3.14	3.33	3.97	4.42
18	1.82	2.87	3.18	3.36	4.00	4.46

Note: These nominal data are based on *in vitro* testing at 37°C and do not take into account lesion resistance.
Ensure full deployment of the stent (see Section 13.5, Operator's Instructions, Deployment Procedure) and confirm the stent sizing angiographically.
*Do not exceed the rated burst pressure (RBP).

15.0 REUSE PRECAUTION STATEMENT

Do not use if sterile barrier is damaged. If damage is found call your Abbott Vascular, Cardiac Therapies representative.

For single patient use only. Do not reuse, reprocess or resterilize.

16.0 PATENTS

This product and/or its use are covered by one or more of the following United States patents: 5,040,548 ; 5,061,273 ; 5,154,725 ; 5,234,002 ; 5,242,396 ; 5,350,395 ; 5,451,233 ; 5,496,346 ; 5,514,154 ; 5,569,295 ; 5,603,721 ; 5,636,641 ; 5,649,952 ; 5,728,158 ; 5,735,893 ; 5,759,192 ; 5,780,807 ; 5,868,706 ; 6,056,776 ; 6,131,266 ; 6,179,810 ; 6,273,911 ; 6,309,412 ; 6,312,459 ; 6,369,355 ; 6,419,693 ; 6,432,133 ; 6,482,166 ; 6,485,511 ; 6,629,991 ; 6,629,994 ; 6,651,478 ; 6,656,220 ; 6,736,843 ; 6,746,423 ; 6,753,071 ; 6,818,247 ; 6,827,734 ; 6,887,219 ; 6,887,510 ; 6,890,318 ; 6,908,479 ; 6,921,411 ; 6,929,657 ; 6,939,373 ; 6,957,152. Other US patents pending. Foreign patents issued and pending.

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Graphical Symbols for Medical Device Labeling

Manufacturer	REF Catalogue Number	F French Size
Do not reuse, do not resterilize	STERILE EO Sterilized using Ethylene Oxide	Consult Instructions for Use
Use By	LOT Batch Code	Date of Manufacture
Guiding Catheter	PYROGEN Non-Pyrogenic	Contents (Numeral represents quantity of units inside)
Inner Diameter		

Agency Medical Director Comments

Health Technology Clinical Committee

Cardiac Stents

Cardiac Stents Background

- **PTCA and Stents (BMS and DES) Context**
  - **Technology is not new, but is evolving**
  - **Randomized Studies and Meta-analysis conflict with large observational studies**
  - **70% of stent use is "off label"**
    - Increasingly common are stent use in multiple vessels, multiple stents in a single vessel, or in vessels outside FDA diameters and lengths (Win, JAMA 2007)
    - The majority of patients with PCI have no assessment of MI risk (Lin, JAMA 2008)

State Agency Utilization Criteria for Cardiac Stents

Procedure	UM/UR
PTCA (HCA, LNI, DSHS)	No PA or restrictions
Stents (HCA, LNI, DSHS)	No PA or restrictions
On Label vs. Off Label (DSHS)	Some risk for an audit

Cardiac Stent Procedure Utilization: 2004-2007 Clinical Outcomes Assessment Program (COAP)*

Year	2004	2005	2006	2007
Total PCI Procedures**	**15,158**	**15,330**	**15,686**	**14,164**
No Prior PCI	*10,022*	*10,146*	*10,265*	*9,135*
Repeat Procedures	*5,136*	*5,184*	*5,421*	*5,029*
% Repeat Procedures	*34%*	*34%*	*35%*	*36%*
PCI Procedures with Stents	**13,348**	**14,104**	**14,542**	**13,032**
% stented PCIs	*88%*	*92%*	*93%*	*92%*
Count of All Stents	*18,860*	*19,931*	*21,048*	*19,688*
Count of Bare Metal Stents	*3,224*	*1,408*	*2,122*	*5,214*
Count of Drug-Eluting Stents	*15,636*	*18,523*	*18,926*	*14,474*
% Bare Metal Stents	*17%*	*7%*	*10%*	*26%*

* A program of the Foundation for Healthcare Quality in WA state

** Inpatient and outpatient procedures

Cardiac Stent Procedure Utilization: 2004-2007

	2004	2005	2006	2007
Total Costs*	**$14,263,103**	**$15,505,519**	**$17,218,988**	**$16,544,589**
Total Procedures**	**988**	**1010**	**1040**	**954**
*Bare Metal****	*175*	*80*	*117*	*283*
*Drug-Eluting****	*781*	*919*	*904*	*650*

* Inpatient, outpatient, Medicaid and Uniform Medical Plan as primary and secondary payors
** Procedure codes 36.06, 36.07, 92980, 92981, G0290 and G0291 performed as primary or secondary procedure
*** Excludes patients who received both types in same procedure

Cardiac Stent Procedure Costs and BMS/DES Cost Differential

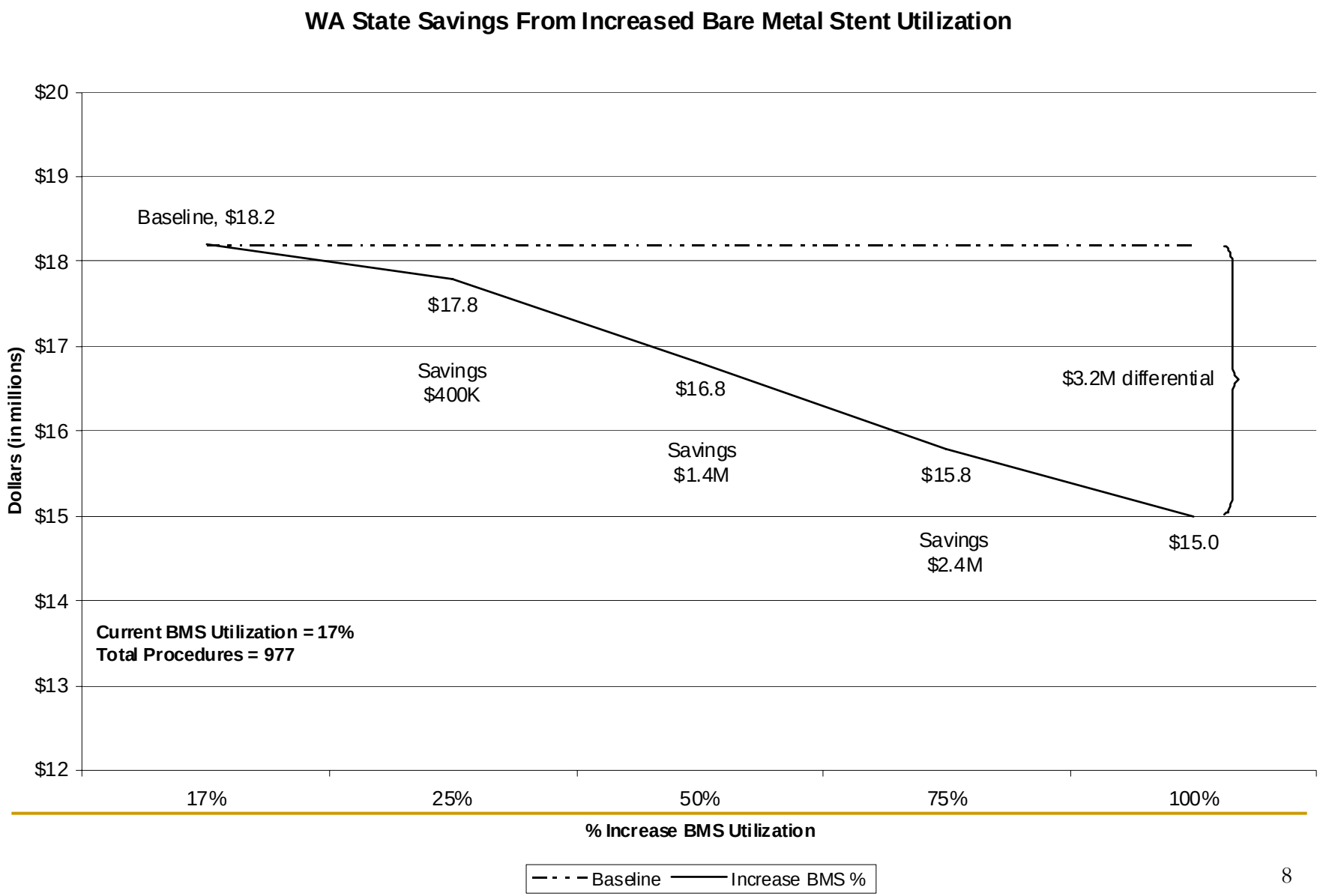
2009 Procedure Costs†	Costs	Differential
Medicaid		
Inpatient		
Bare Metal	$13,024	
Drug-Eluting	$16,670	$3,646
Outpatient		
Bare Metal	$4,863	
Drug-Eluting	$6,615	$1,752
Uniform Medical Plan		
Inpatient		
Bare Metal	$22,360	
Drug-Eluting	$26,497	$4,137
Outpatient		
Bare Metal	$13,038	
Drug-Eluting	$17,345	$4,307

† Inpatient costs based on APDRGs 852 and 854. Outpatient costs based on weighted facility fees for CPT code 92980 and HCPCS code G0290

Cardiac Stents

- **Other Plans and Medicare**
  - Medicare National Coverage Decision
    - Covers PCI with and without stent (FDA approved protocols) for a single vessel
    - Medicare local covers ≤ 1 DES or additional vessels
  - Other Health Technology Assessments
    - **Aetna:** Members with angina and >50% stenosis
    - **Cigna:** DES for symptomatic disease, however; DES for E&I including acute MI, unprotected LMCA and SVG – not covered
    - **VA:** Covers PCI for one or more arteries for FDA and conditions may be considered for cost sharing
    - **Ontario HTA:** two of following 1) long lesions {>20mm}, 2) narrow lesions {<2.75mm}, 3) diabetes, to target higher risk clients

Potential Cost Change



Cardiac Stents: Summary

- **State Agencies**
  - **Safety**
    - The safety is evolving and we need be transparent with the benefits vs. the risks
    - Better understand the NNH (short and long term thrombosis, fracture, and revascularization risks)
  - **Efficacy and Effectiveness**
    - Discuss the NNT (mortality, morbidity, MI, vs. Target Vessel Revascularization) with BMS vs. DES
  - **Special Populations**
    - Determine how to encourage use in at risk populations with higher effectiveness and help to encourage better informed risks and options
  - **Cost**
    - Discuss and be transparent in the value and the cost effectiveness BMS vs. DES

Washington State Health Care Authority

Cardiac Stents: Recommendations

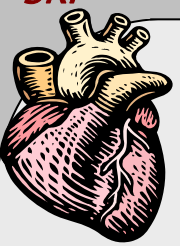
- Non-emergent PCI be subject to some form of prior authorization or quality controls to ensure effective "on label" & evidence based "off label" use (perhaps using the JACC Appropriate Criteria for Coronary Revascularization)

- Coverage limitation for DES should be limited to high risk clients (e.g., diabetes).

- Quality controls should ensure the client has adequate informed consent of safety, revascularization, risks, benefits, and options


Spectrum Research, Inc.
Bringing Evidence to Light

SRI



Coronary Artery Disease: Comparison of Drug Eluting Stents (DES) with Bare Metal Stents (BMS)

Health Technology Clinical Committee Meeting
Washington State Health Technology Assessment Program

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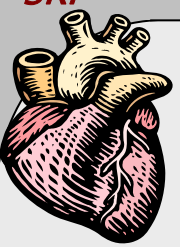
May 8, 2009

SPECTRUM RESEARCH



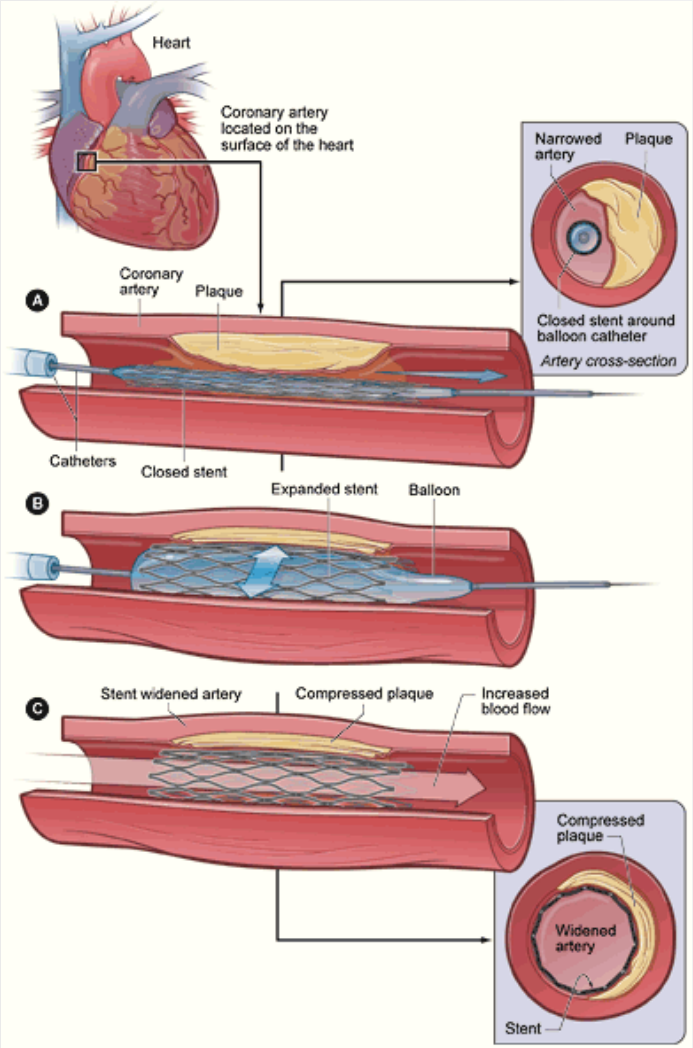
Scope of Report

This report critically summarizes relevant health technology assessments and recently published research comparing drug-eluting stents (DES) with bare metal stents (BMS) for the treatment of coronary artery disease.

The report focuses on the highest quality evidence available based on systematic review of the literature

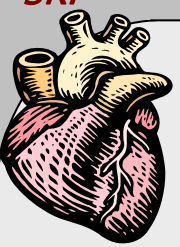
SRI

Background
Stent placement in coronary artery disease



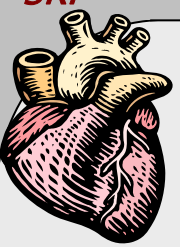
- Stents were designed to address narrowing of coronary vessels caused by plaque
- A catheter is inserted across the lesion
- Balloon inflation expands the stent and compresses plaque
- The stent remains to act as a scaffold to keep the lumen open allowing increased blood flow
- New endothelial lining forms over the stent

SPECTRUM RESEARCH



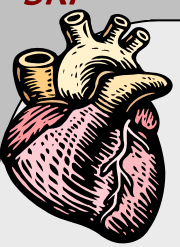
Background
Coronary stents – Historical development

- PTCA (balloon angioplasty) was first described in 1977. Although initially it decreased lumen narrowing, injury to the vessel walls led to acute closure (6%-8%) and restenosis (30%-50%).
- Bare metal stents (BMS) were introduced in 1986 (and approved by the FDA in 1993) as a way to overcome the limitations of PTCA.
  - BMS created a more uniform vessel opening, leaving in place a metal scaffolding to prevent closure.
  - Inflammatory reaction and exaggerated cell proliferation resulted in re-stenosis in 20%-25% of patients within 6 months.



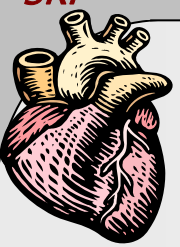
Background
Coronary stents – historical development

- Restenosis is a potentially serious problem
  - Morbidity and mortality rates in one study were 9.5% and 0.7% respectively (Chen, 2006)
- Drug-eluting stents (DES) were designed to prevent neointimal hyperplasia and subsequent restenosis
  - A polymer coating applied to the metal stent releases anti-proliferative drugs into the local environment
- Anti-platelet therapy is used with BMS and DES
- FDA approval granted for 9 BMS and 4 DES designs



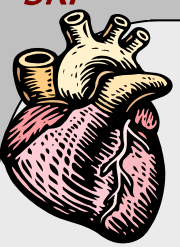
Background
Currently approved FDA DES

Sirolimus-eluting (SES)	CYPHER (Cordis)
Paclitaxel-eluting (PES)	TAXUS (Boston Scientific)
Zotarolimus-eluting (ZES)	Endeavor (Medtronic)
Everolimus-eluting (EES)	XIENCE (Promus) (Abbott)



Background
Currently approved FDA Stents

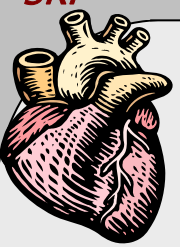
- Indications (FDA)
  - Treatment of symptomatic ischemic disease in patients with *de novo* lesions in native coronary arteries
- Contraindications
  - Hypersensitivity to stent components (including drugs used in DES, polymers and metals used)
  - Patients in whom anti-platelet or anti-coagulation therapy is contraindicated
  - Lesions that don't allow for complete balloon inflation



Key Questions: DES vs. BMS

In patients with CHD undergoing stenting of coronary vessels:

1. What is the evidence of efficacy and effectiveness of drug-eluting (DES) versus bare metal stents (BMS)
    - Including any effects on special populations, such as patients with and without diabetes, after myocardial infarction and not after myocardial infarction; and in different vessel and lesion characteristics.
2. What is the evidence related to safety profile of DES versus BMS
    - Including in patients with and without continuation of anti-platelet medications
3. What is the evidence of cost effectiveness and cost implications of DES versus BMS
    - Including any effects of pharmacologic therapy and reintervention

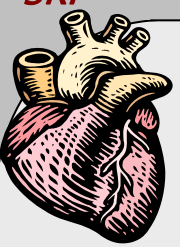


Inclusion Criteria

Previously published HTAs or similar reports directly comparing DES with BMS

Meta-analyses published after these

Studies published after HTAs or meta-analyses



Inclusion Criteria - New studies

Patient population:

Patients with CAD undergoing stenting of native coronary vessels

Intervention/Comparator:

FDA-approved DES compared with FDA-approved BMS

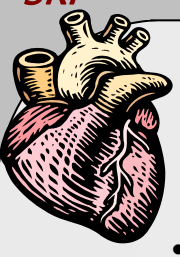
Study design:

Randomized controlled trials (RCTs) and comparative studies with concurrent controls which compared DES with BMS; case series only for safety context

Full formal economic studies

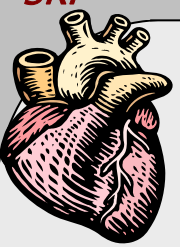
Publications:

Full-length studies published in peer-reviewed journals in English (no meeting abstracts, proceedings, supplements)



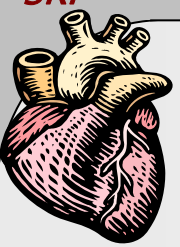
Literature Search

- Electronic databases and HTA sites searched from 2007 - mid-January, 2009 using a systematic approach
- Vast literature: 304 potentially relevant citations
- 10 previous health technology assessments or similar reports
- 12 meta-analyses or pooled analyses, one of which was of non-randomized studies
- 13 reports of long-term follow-up or subanalyses to previous RCTs or new RCTs found
- 26 non-randomized or registry studies
- 1 full economic study and one systematic review



Primary data source overview

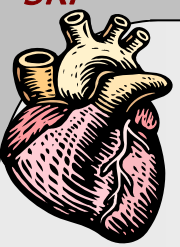
- HTAs or similar reports
  - 2 (Hill, ECRI) did own meta-analysis of RCTs
  - 1 (KCE) used results from previous meta-analyses
  - 1 (Ontario) did meta-analysis on registry studies
  - 4 (Hill, KCE, Ontario, FinOHTA) did full economic analyses
- Meta-analyses published after HTAs
  - 1 meta-analysis in general populations included 38 RCTs, N = 18,023 (Stettler 2007 Lancet **370**(9591): 937-48)
  - 1 meta-analysis with outcomes for diabetic patients separated and length of anti-platelet therapy evaluated from 35 RCTs, N = 14,799 (Stettler 2008 BMJ **337**: a1331)



Meta-analysis – Stettler 2007

	PES vs. BMS	SES vs. BMS	SES vs. PES
No. Trials*	8	17	15
No. Centers	1-3 (4 trials) 38-73 (4trials)	1-4 (9 trials) 8-19 (3 trials) 20-53 (4 trials)	1-5 (14 trials) 90 (1 trial)
No. Patients	5138	5818	8719
Follow-up (months) 12	2	7	4
24	2	4	4
36	1	1	6
48	3	5	1

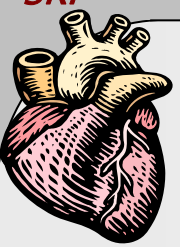
*includes one study with 3 arms: SES, PES and BMS



Meta-analysis – Stettler 2007

Demographics

	PES vs. BMS	SES vs. BMS	SES vs. PES
Age (range)	61 - 66 years	59 - 73 years	56 - 68 years
% Male (range)	69% - 90%	34% - 85%	64% - 82%
%Diabetes			
General trials	11%-32%	13%-31%	0%-34%
DM specific	-	100% (3 trials)	100% (3 trials)



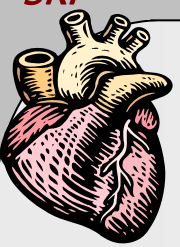
Meta-analysis – Settler 2007

Indications (number of trials)

	PES vs. BMS	SES vs. BMS	SES vs. PES
Total No. Trials	**8**	**17**	**15**
Stable or unstable angina	**6**	**10**	**7**
Acute coronary syndrome	**-**	**3**	**2**
Silent ischemia	**5**	**6**	**5**
Acute MI	**3**	**5**	**5**

Trial quality summary (38 trials)

- 29 with appropriate concealment
- 28 had blinded adjudication
- 31 had all patients included in ITT analysis
- 22 met all three of these criteria

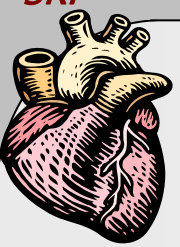


Outcomes reported in meta-analyses

Focus: longer term (to 4 years)

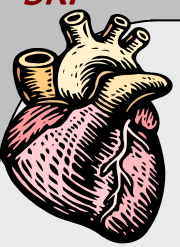
- **Efficacy and effectiveness**
  - Death
  - Cardiac death
  - Myocardial infarction
  - Target lesion revascularization
- **Safety**
  - Thrombosis
  - Late stent thrombosis

Different perspectives: Is the role of stenting to keep the vessel open or to prevent death and MI?



Definition of revascularization and context

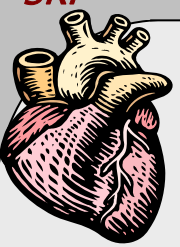
- **Revascularization**
  - Refers to *repeat* revascularization with PCI or CABG to address narrowing (restenosis) of the vessel from scar tissue growing beneath the new endothelial layer
  - Clinical symptom driven vs. angiographically driven
  - Trials frequently do not document angina recurrence
  - TLR = any repeat intervention (PCI or CABG) of the target lesion or vessel for restenosis or complications of target lesion (5 mm proximal or distal) [Stettler]



Key Question 1 – Efficacy and effectiveness

What is the evidence of efficacy and effectiveness of drug eluting (DES) versus bare metal stents (BMS)?

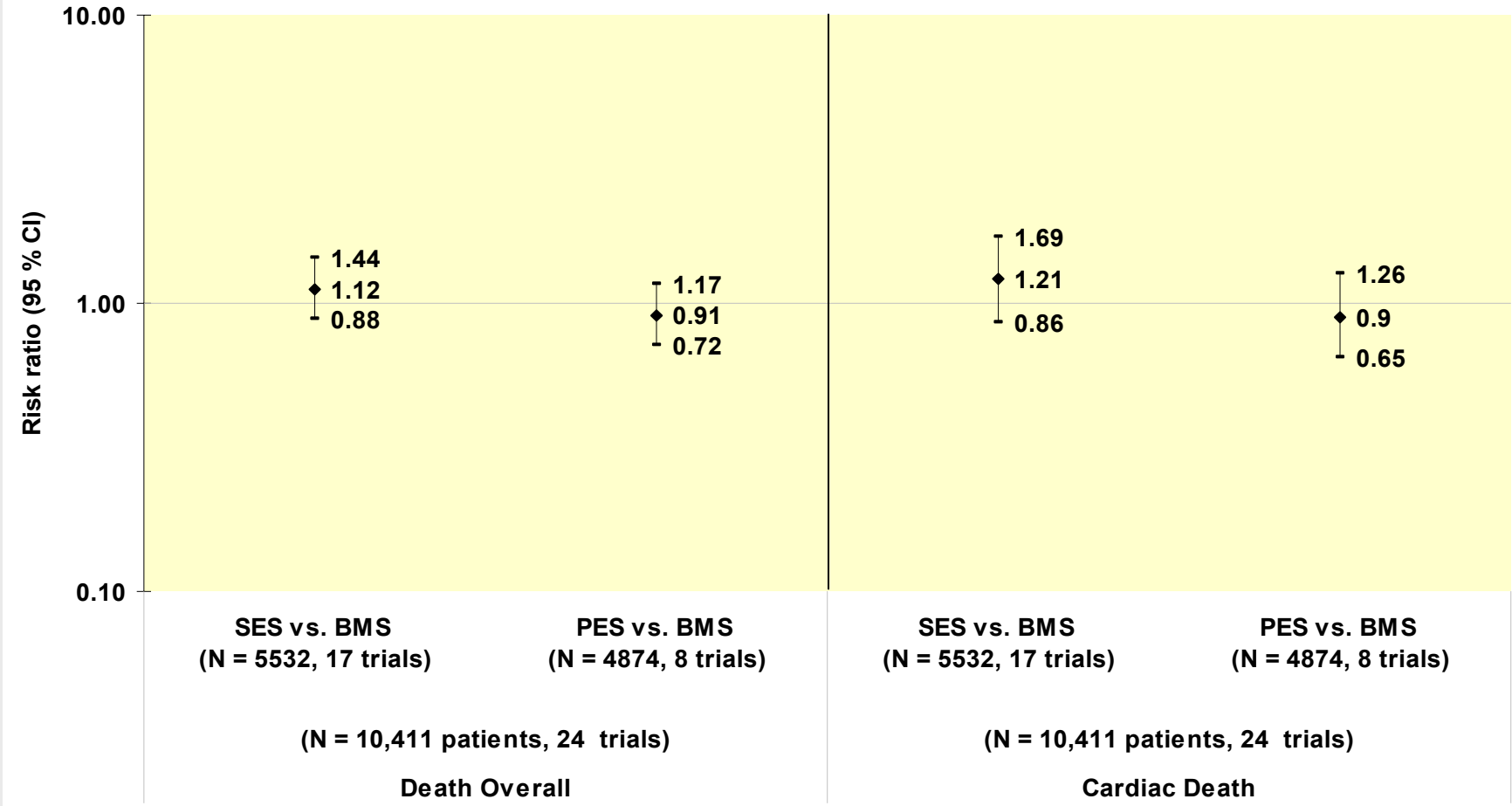
- Efficacy
  - HTA conclusions based on RCTs/MAs
  - Meta-analysis data (Stettler 2007 and 2008)
- Effectiveness
  - HTA conclusions; one with meta-analysis
  - Summary of non-randomized studies



Key Question 1 – Efficacy
Summary of HTA findings

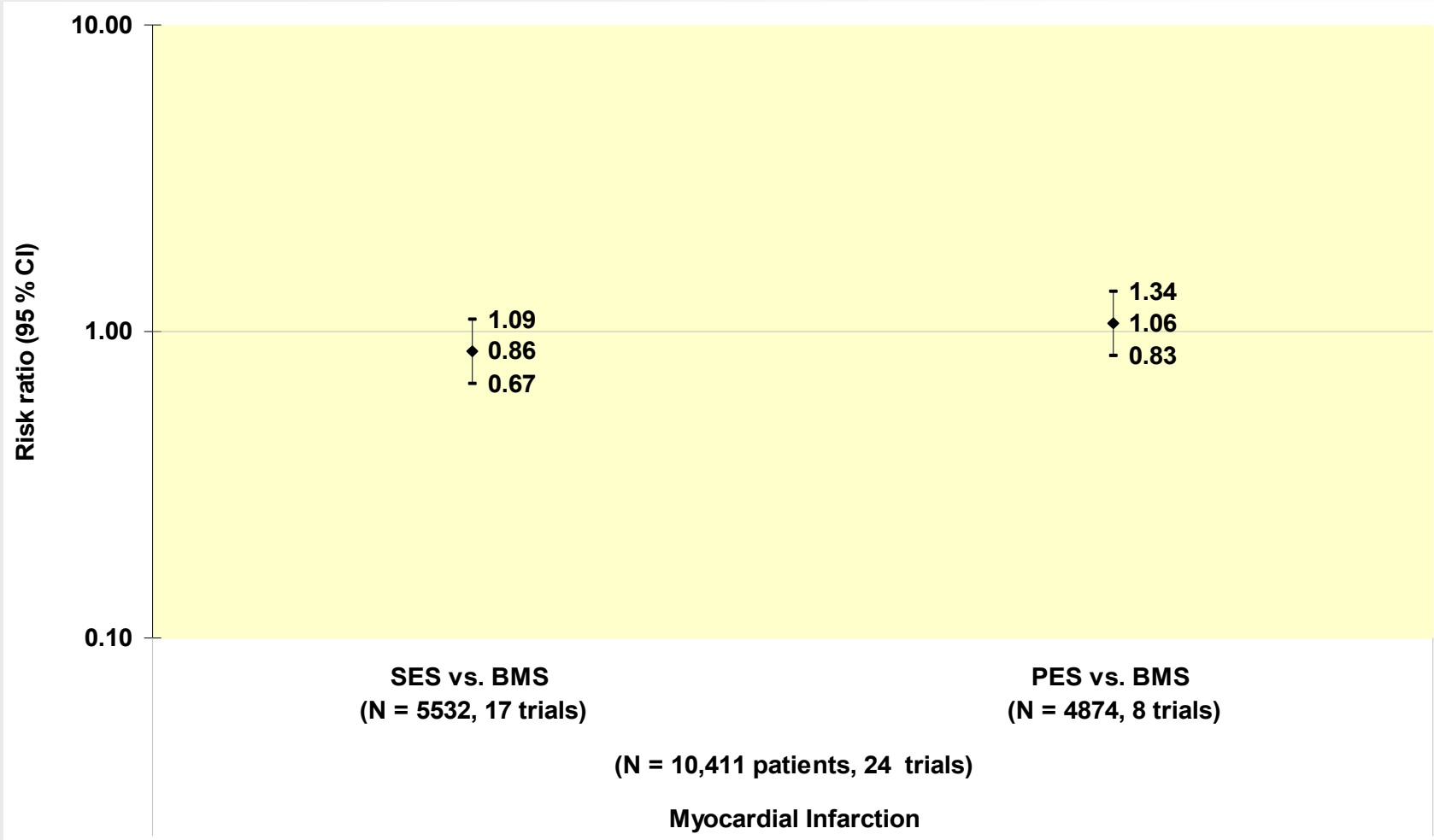
- Death and cardiac death
  - No statistically significant difference in overall mortality or cardiac mortality
- Myocardial infarction
  - No statistically significant difference in myocardial infarction
- Target lesion/vessel revascularization
  - DES consistently associated with decreased risk of revascularization compared with BMS

Key Question 1- Meta-analysis findings
Death and Cardiac Death (0 - 4 years)



Rates: Death-DES 4.1%, BMS 4.7%; Cardiac Death - DES 2.4%, BMS 2.7%

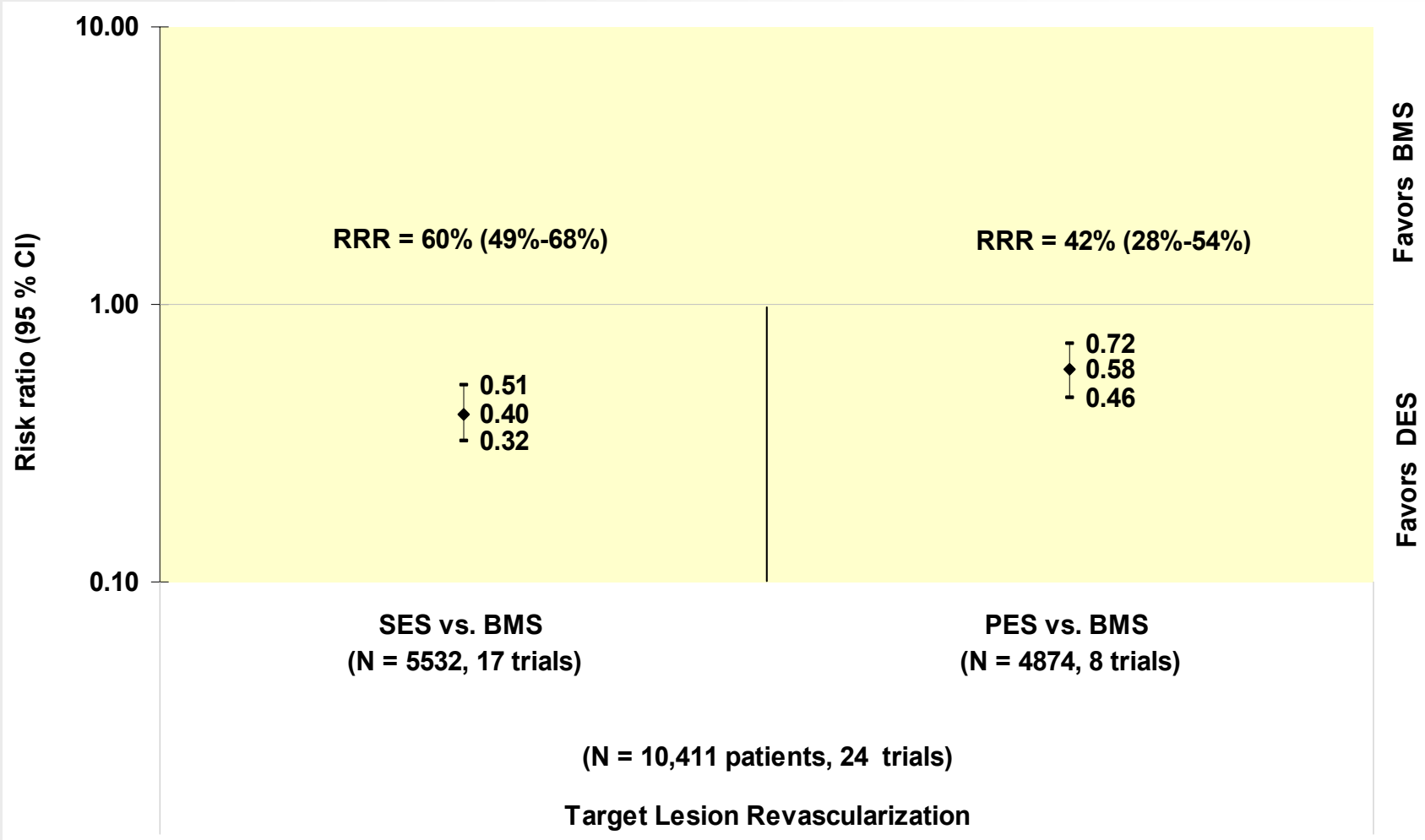
Key Question 1- Meta-analysis findings
Myocardial Infarction (0 – 4 years)



Rates: DES 4.5%, BMS 5.2%

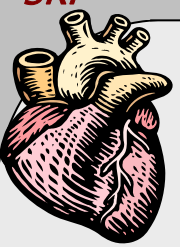
SRI

Key Question 1- Meta-analysis findings
Target Lesion Revascularization (0 – 4 years)



Rates: DES 7.9%, BMS 19%; RD 11.1%

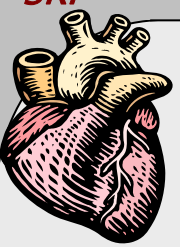
SPECTRUM RESEARCH



Key Question 1 – Effectiveness
Nonrandomized Studies

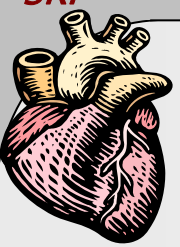
- **HTA conclusions on effectiveness – nonrandomized studies**
  - Mortality and MI rates do not differ between stent types
  - In HTA meta-analysis, substantial heterogeneity is noted
  - Rates of revascularization are lower for DES
- **Rates from recent nonrandomized studies: > 1year follow-up**

Outcome	DES	BMS
Death (8 studies)	4.5% - 8.5%	6.1% -17%
MI (5 studies)	1.7% - 12.7%	2.0% – 11.5%
TLR/TVR (13 studies)	5.2% - 14.2%	8.1% - 24.4%



Key Question 1- Effectiveness
Nonrandomized Studies

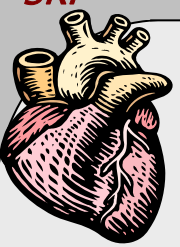
- Recent nonrandomized studies:
  - **Death:** Mixed results - No statistically significant difference in 5 studies; Statistically significant difference in 3 favoring DES in those with > 1 year follow-up
  - **Myocardial infarction**: Mixed results - No statistically significant difference in at any time in 7 studies; Statistically significant favoring DES in 3 studies for at least one time point
  - **TLR or TVR:** 13 studies reported statistically significant lower rates for DES at one time point



Key Question 2 – Safety

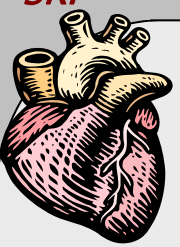
What is the evidence related to safety profile of DES versus BMS

- **Studies**
  - HTA conclusions based on RCTs/MAs
  - Meta-analysis data (Stettler 2007 and 2008)
  - Summary of non-randomized studies
- **Outcomes**
  - Stent thrombosis
  - Late stent thrombosis



Key Question 2 – Safety
Summary of HTA findings

- Most previous HTAs indicate that there is no statistically significant difference between DES and BMS with regard to risk of stent thrombosis
- 1 review focused on safety concluded that the majority of evidence suggested an increased risk with DES
- 2 reports concluded there was significantly higher risk after 1 year with DES
- Stent thrombosis is a rare event; studies may have been underpowered to detect a difference

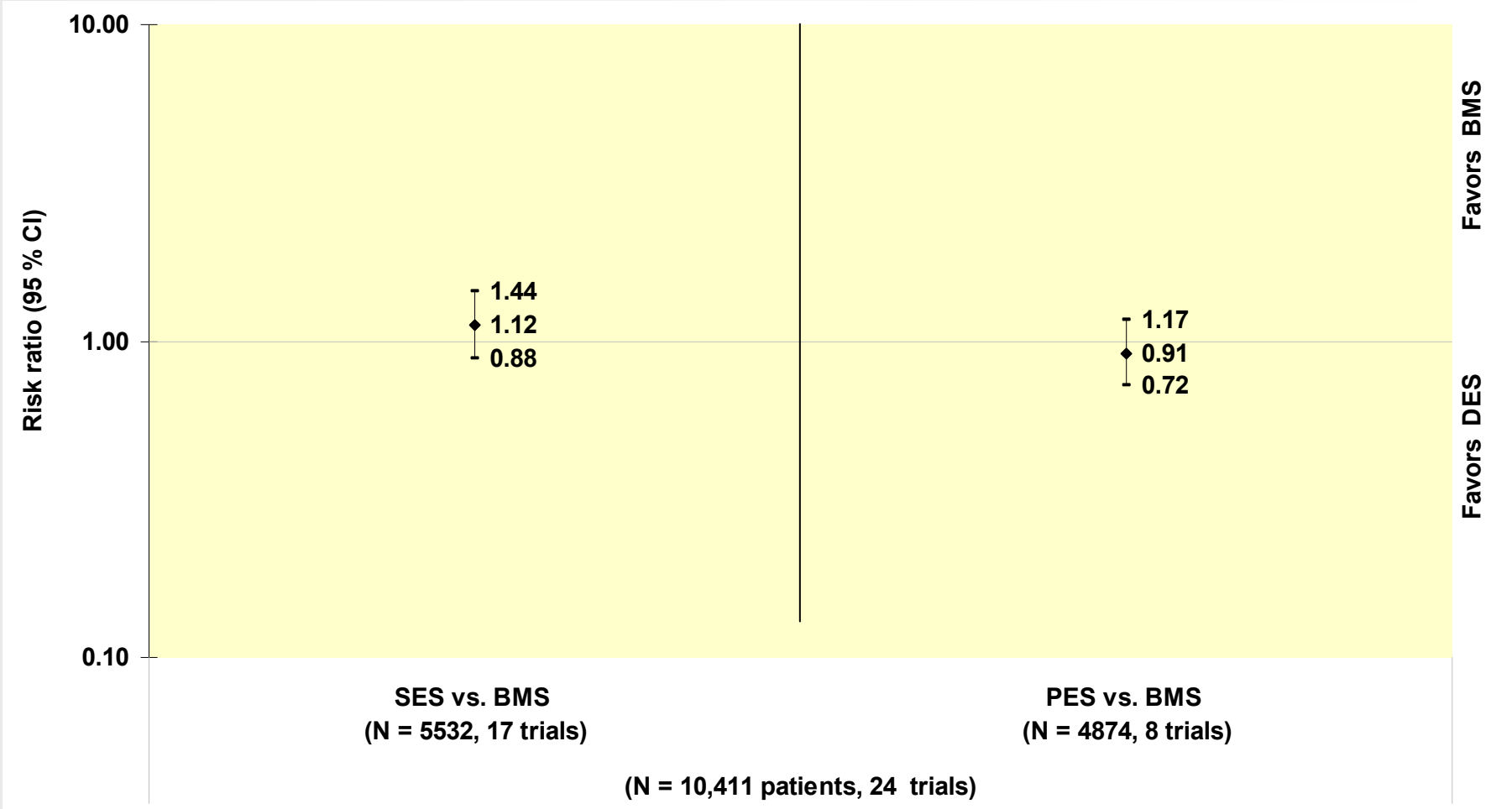


Key Question 2
Summary of HTA findings

- Recent HTAs discussed the 2006 FDA panel review
- **FDA conclusions**:
  - DES for off-label indications was related to increased incidence of stent thrombosis, MI and death
  - Discontinuation of anti-platelet therapy was an independent risk factor
  - Risk of thrombosis does not outweigh advantage of DES over BMS in reducing repeated revascularization when used for approved indications

Key Question 2- Meta-analysis findings

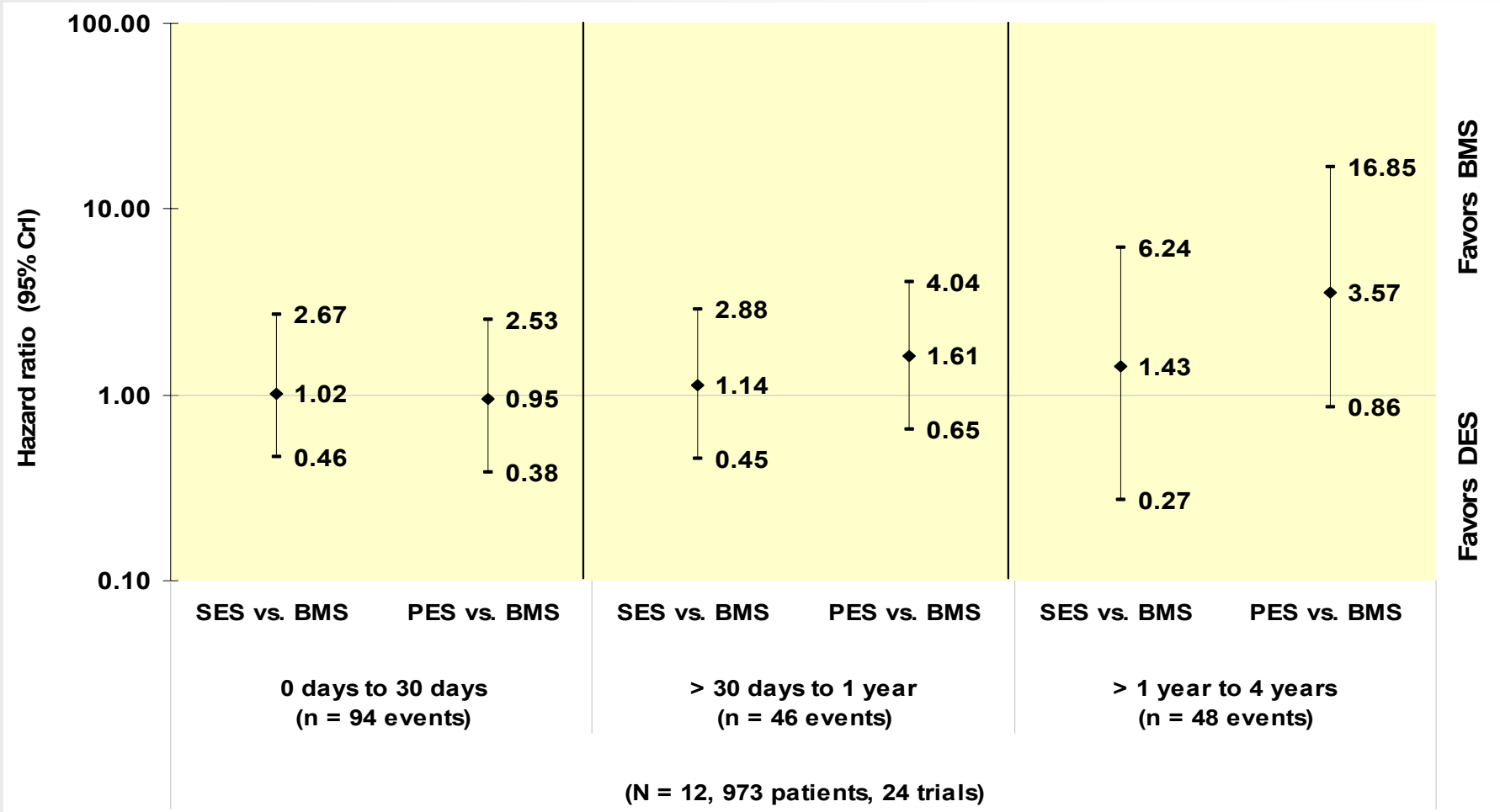
ARC defined definite stent thrombosis (0 – 4 years)



Rates: DES 1.5%, BMS 1.2%

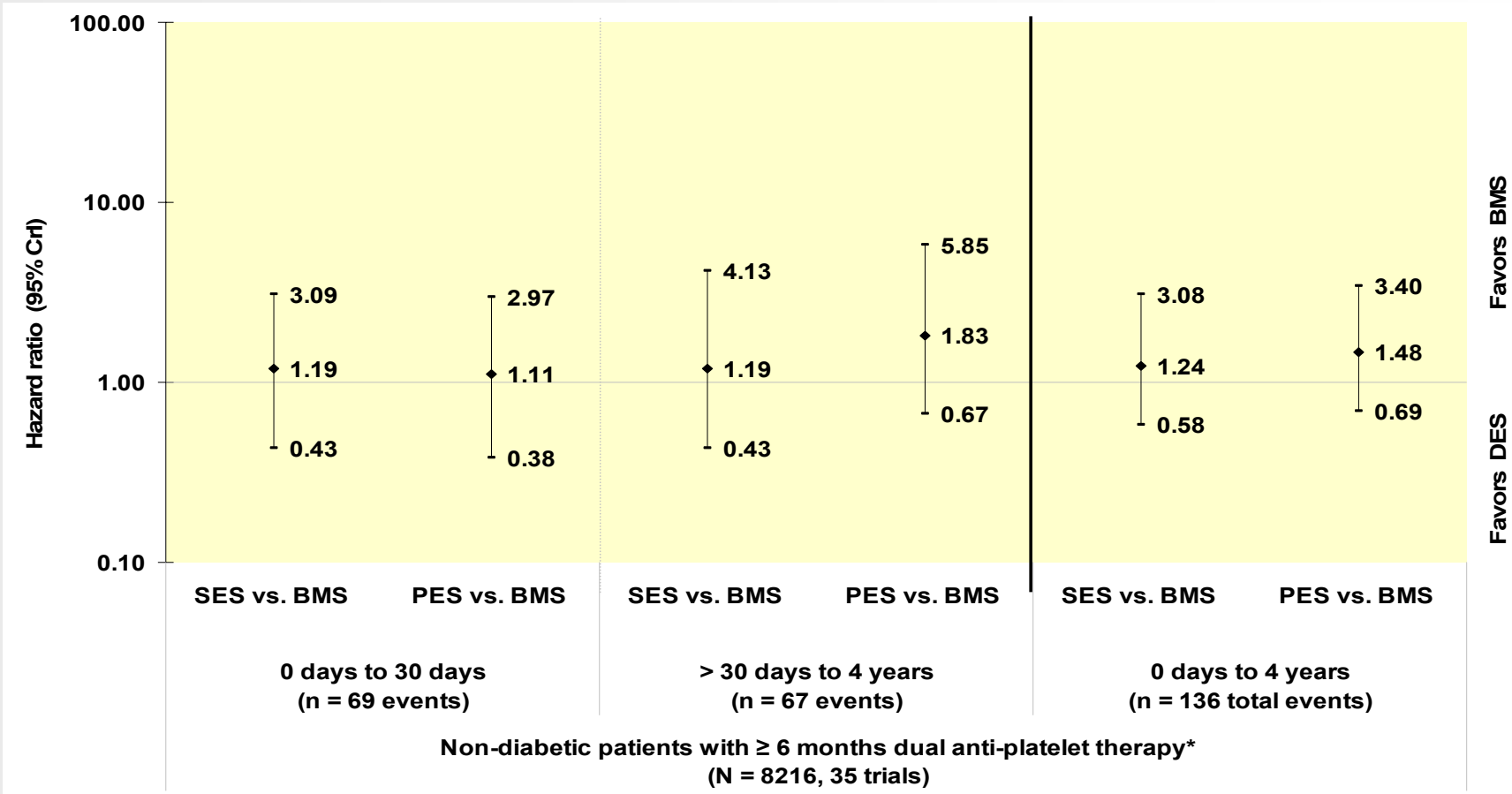
Key Question 2- Meta-analysis findings

ARC defined definite stent thrombosis over time

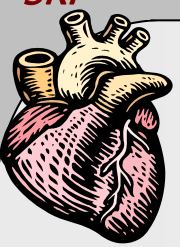


Key Question 2- Meta-analysis findings
ARC defined definite stent thrombosis over time

Stettler 2008: Non-diabetic patients with ≥ 6 months dual anti-platelet therapy



* Precise number of patients and trials for restricted analysis in patients with ≥ 6 months of dual anti-platelet therapy is not provided.



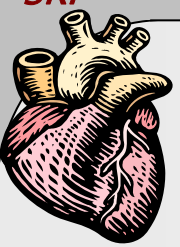
Key Question 2 – **Stent thrombosis**

Recent nonrandomized studies

- Rates from 10 recent nonrandomized studies: DES 0% - 2.9%, BMS 0.1% - 3.5%; only 1 reported statistically significantly higher rates for very late stent thrombosis for DES.

All studies

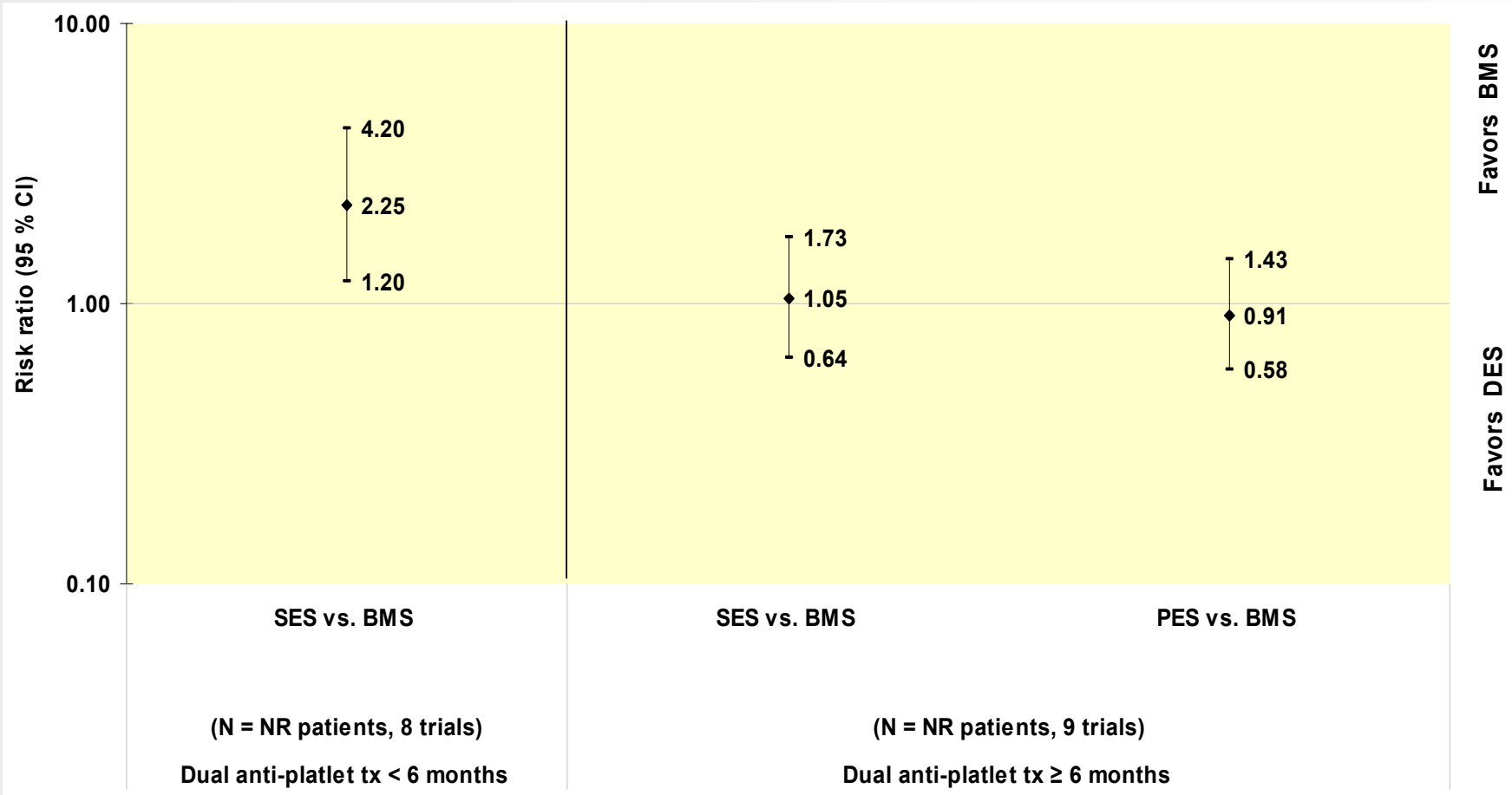
Studies, including MAs, may be underpowered for evaluation of stent thrombosis overall and late stent thrombosis in particular



Key Question 1 - Efficacy, Effectiveness
Special populations: Diabetic patients

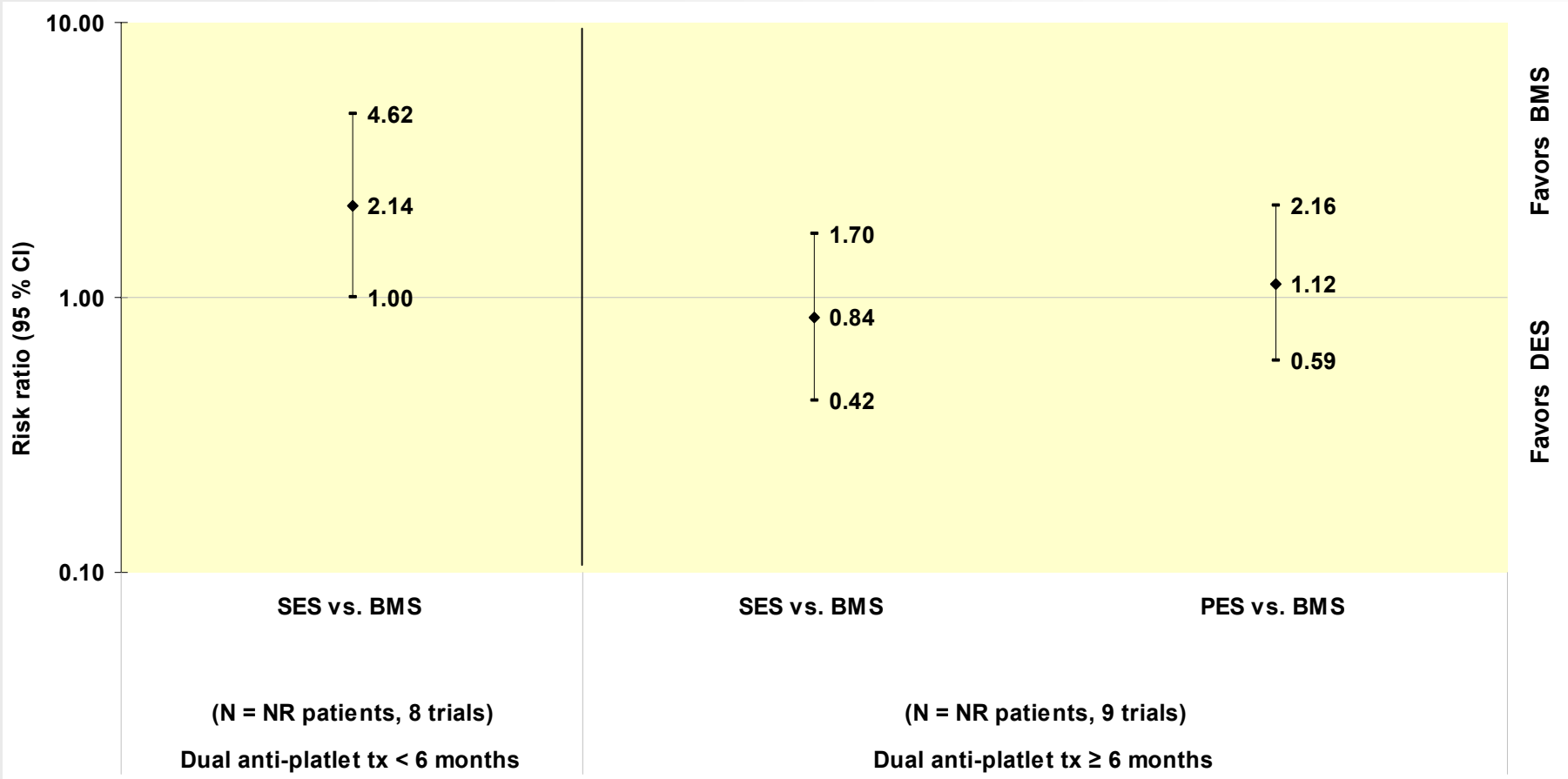
- HTA Conclusions – Efficacy in Diabetic patients
  - Previous HTAs did not provide many data or conclusions regarding special populations
  - 2 HTAs reported on mortality, one concluded there was no difference in mortality, the other did, but the original MA cited did not show a difference
  - None provided data on MI
  - 3 concluded that TLR/TVR were significantly lower with DES placement vs. BMS in diabetic patients

Key Question 1 - Meta-analysis (Stettler 2008)
Diabetic patients – Death (0 – 4 years)



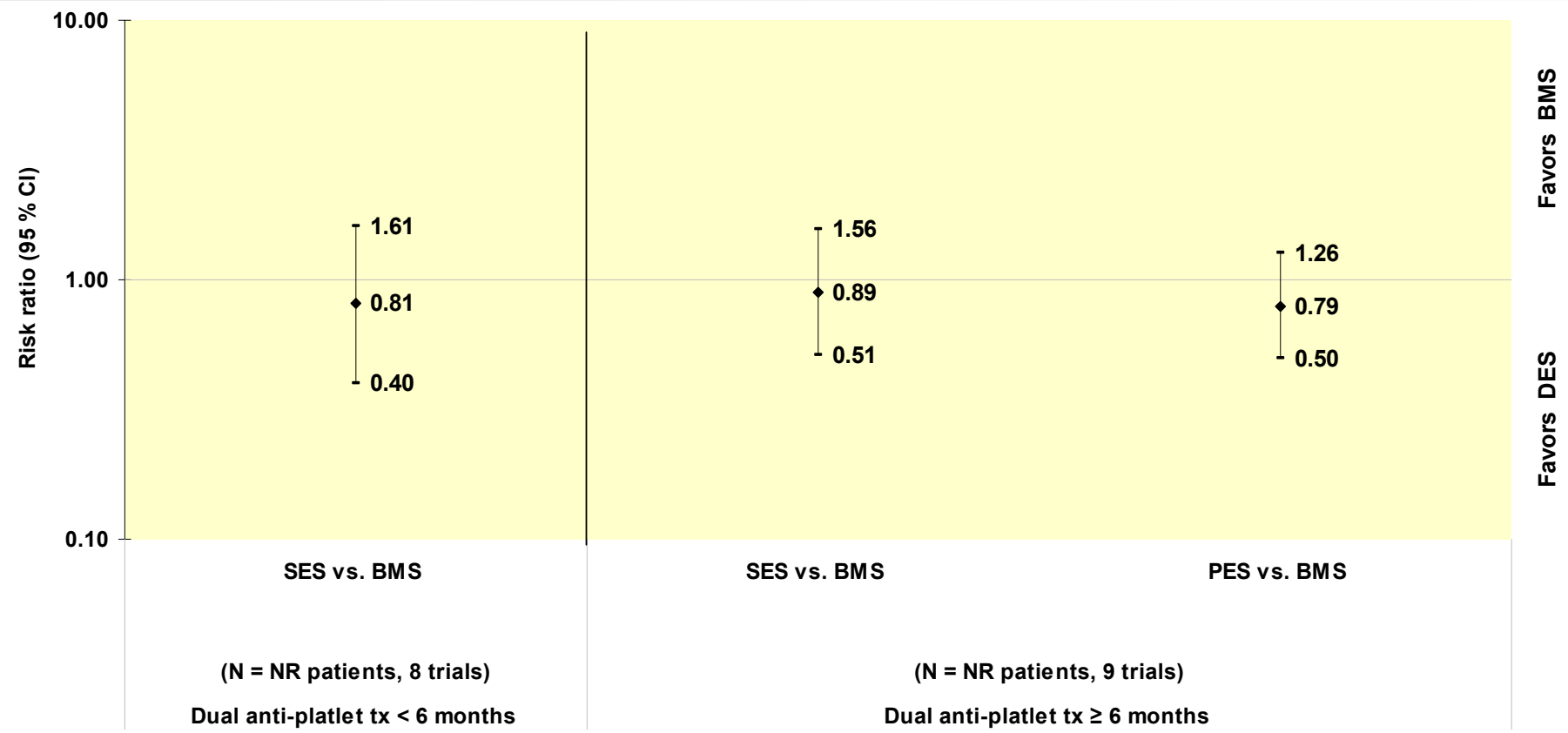
NR = N for trials and patients not provided

Key Question 1 – Meta-analysis
Diabetic patients: Cardiac Death (0 – 4 years)



NR = N for trials and patients not provided

Key Question 1 – Meta-analysis
Diabetic patients: Myocardial Infarction (0 – 4 years)



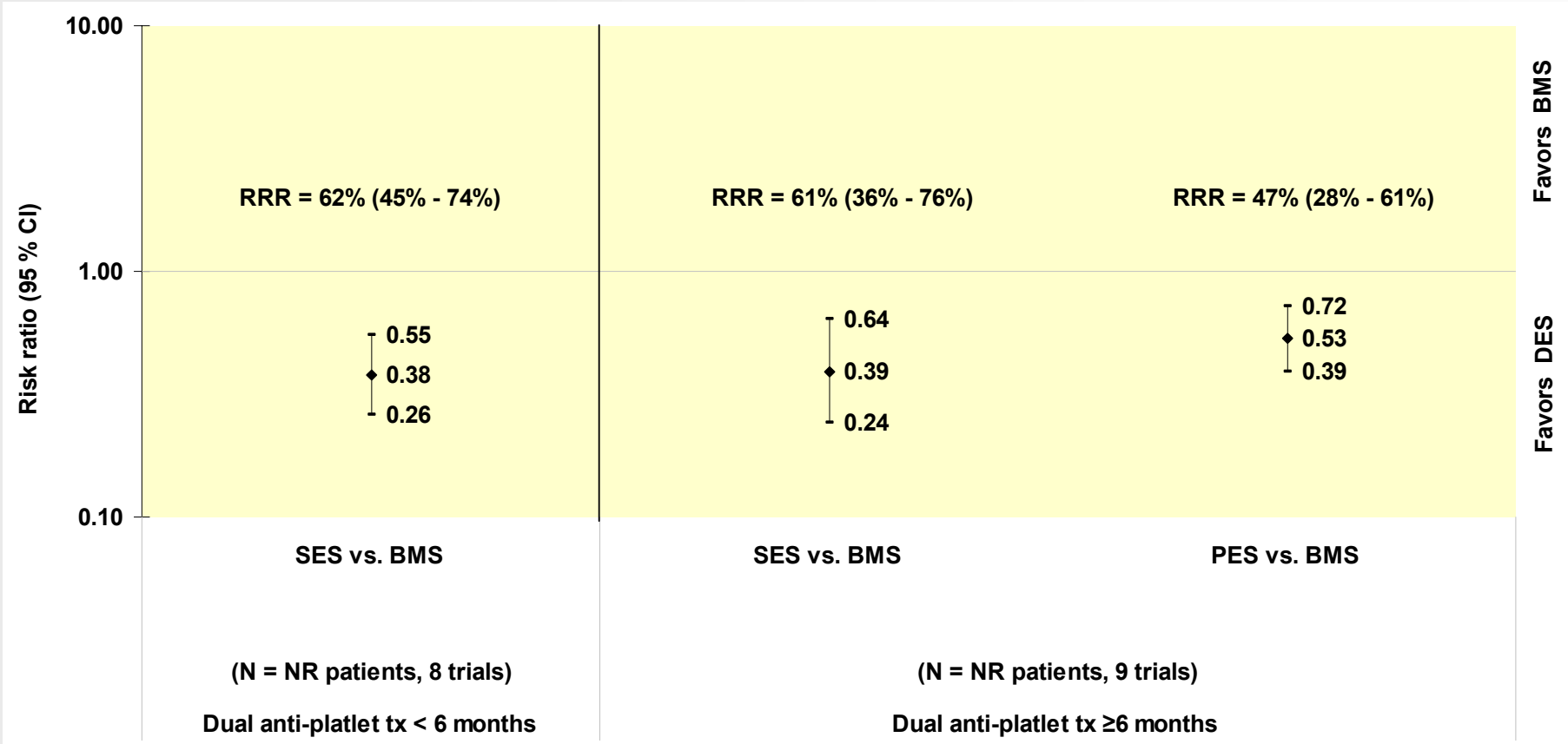
NR = N for trials and patients not provided

MI Rates in patients with ≥ 6 months tx: DES 5.8% BMS 7.4%

SPECTRUM RESEARCH

SRI

Key Question 1 – Meta-analysis
Diabetic patients: TLR (0 – 4 years)

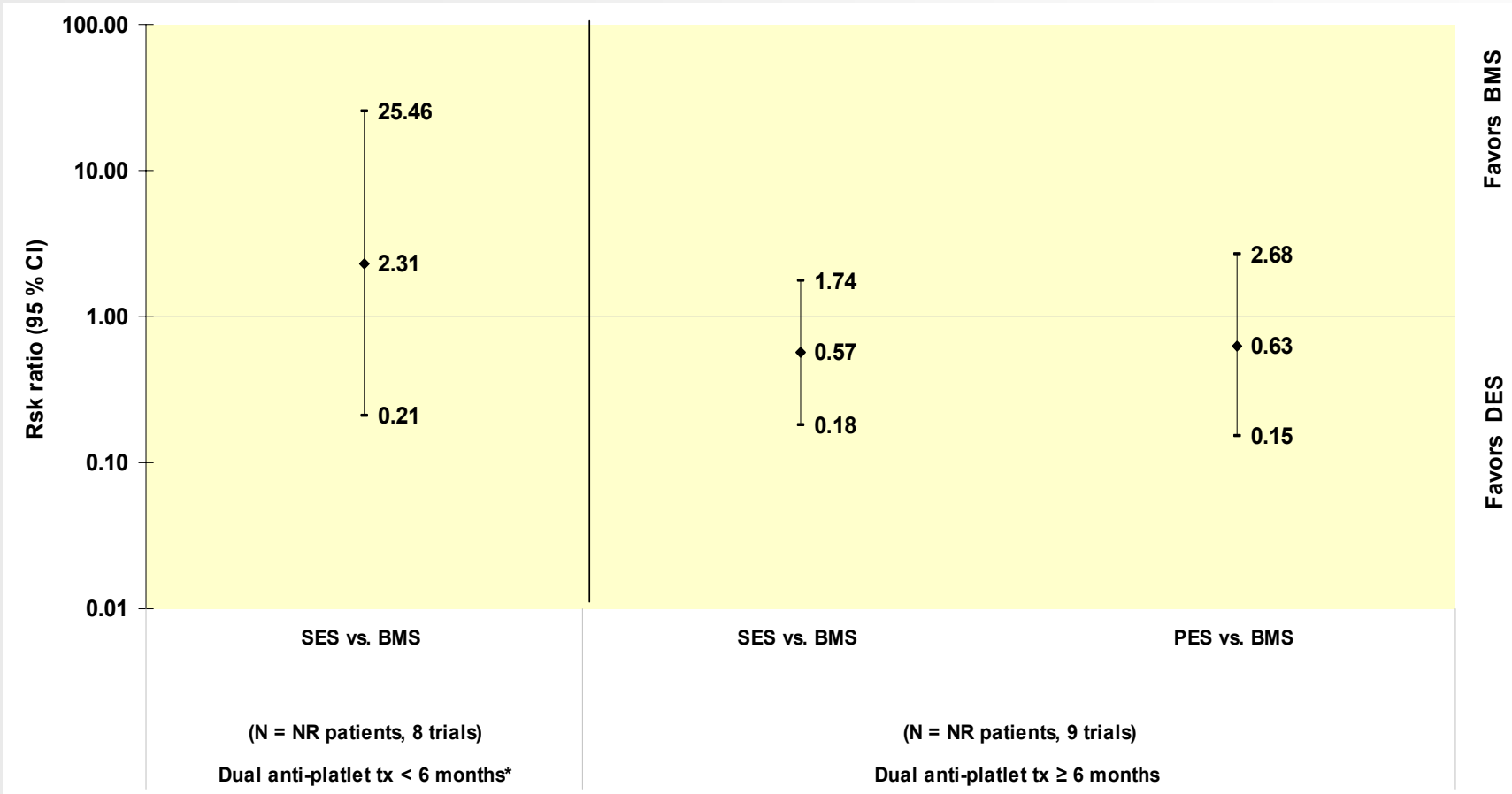


NR = N for trials and patients not provided

Rates in patients with ≥ 6 months tx: DES 9.7% BMS 22%

SPECTRUM RESEARCH

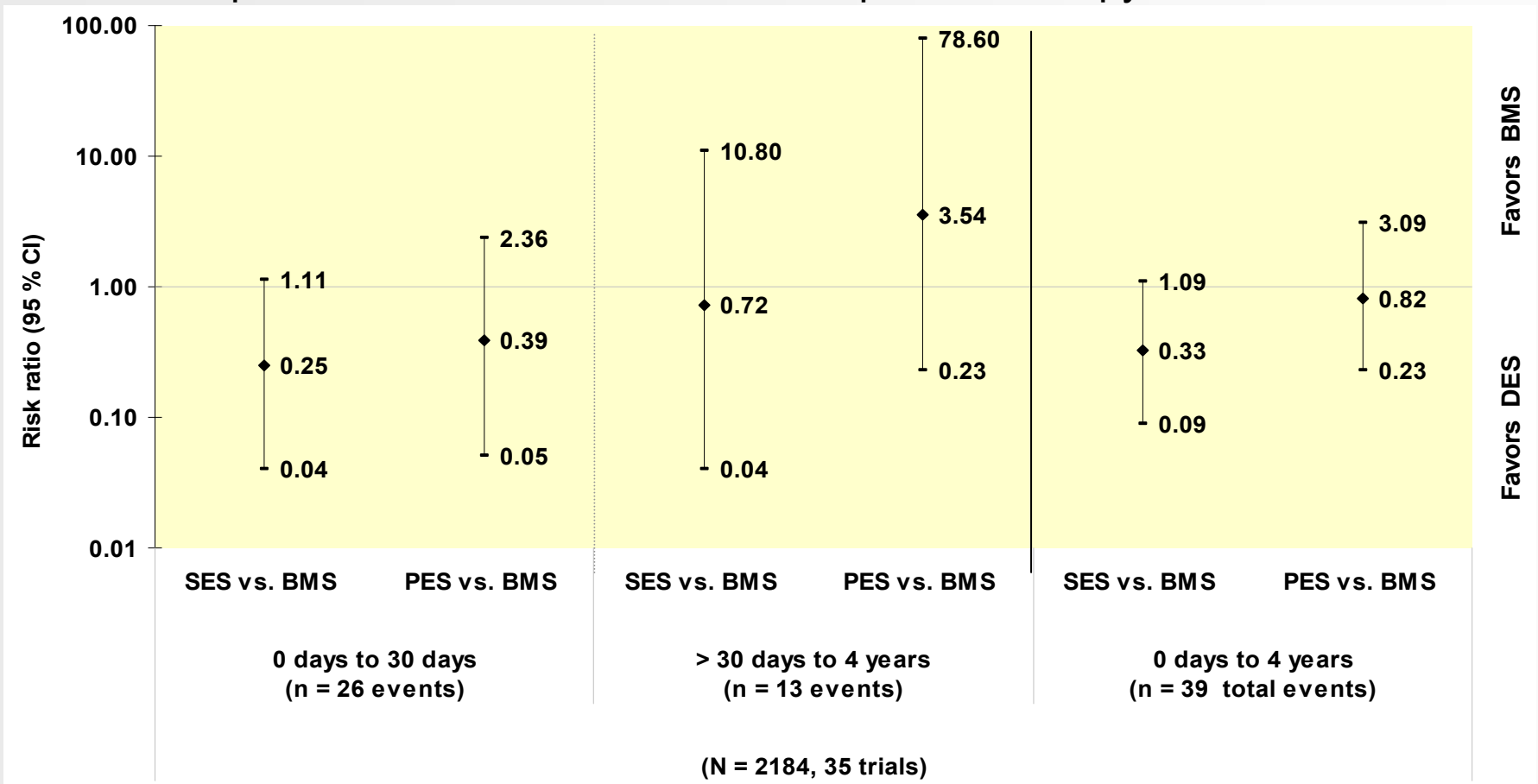
Key Question 2 – Safety (Meta-analysis)
Diabetic patients
ARC definite stent thrombosis (0 - 4 years)

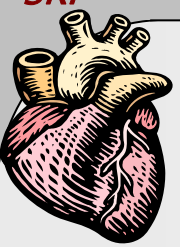


*** Based on 1 trial of patients with < 6 months therapy**

Key Question 2 – Safety, Meta-analysis
Diabetic patients – Stent thrombosis timing

Diabetic patients with ≥ 6 months dual anti-platelet therapy

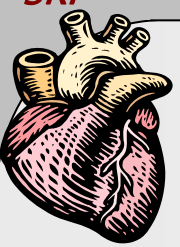




Key Question 1 – **Diabetic patients Nonrandomized studies**

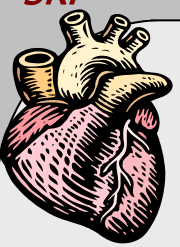
HTA conclusions regarding effectiveness

- mortality
  - 1 report concluded there was no difference in mortality between DES and BMS at 2 years (based on 1 registry study)
  - Ontario meta-analysis:
    - DES recipients had statistically significant lower mortality at 6 months. Difference remained significant from 7-24 months only among those who had had a prior MI



Key Question 1 and 2 – **Diabetic patients Nonrandomized studies**

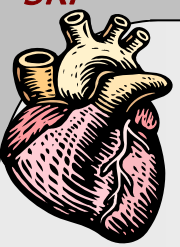
- HTA conclusions - TLR
  - 1 report concluded rates were significantly lower for DES recipients
  - Ontario meta-analysis:
    - DES recipients without prior MI had significantly lower TLR; difference was not significant in patients with prior MI
- HTA conclusions – thrombosis
  - 1 report suggested that patients more likely to benefit from DES (diabetes, small vessels, chronic renal disease) were also more likely to develop stent thrombosis



Key Question 1 and 2 –**Diabetic patients Nonrandomized studies**

- Rates from recent nonrandomized studies with ≥ 1 year follow-up

Outcome	DES	BMS
Death (2 studies)	6.2% - 10.2%	8.0% -12.3%
MI (2 studies)	4.8% - 9.1%	4.7% – 11.5%
TLR/TVR (2 studies)	5.1% - 12.8%	8.4% - 14.4%
Thrombosis (2 studies)	1.1% - 2.4%	0.7% - 3.2%



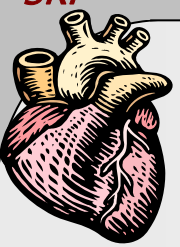
Effectiveness in elderly populations – New AHRQ funded nonrandomized study

- Linked Medicare and ACC–NCDR data for 262,700 patients ≥ 65 years old; focus on outcomes at 30 months
  - Statistically significant decrease (adjusted) in death, MI with DES
  - No difference in overall TLR rates after risk adjustment
- Data from uncorrected proof published online March 28, 09

  Formal critical appraisal and incorporation for next review

Adjusted rates for outcomes at 30 months

	DES (n =217,675)	BMS (n = 45,025)	Difference
Mortality	13.5%	16.5%	3%
MI	7.5%	8.9%	1.4%
TLR	23.5%	23.4%	0.1%

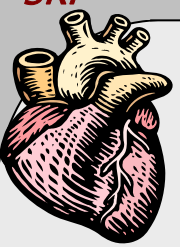


Key Question 3

What is the evidence of cost effectiveness and cost implications of DES versus BMS – including any effects of pharmacologic therapy and re-intervention?

Economic evaluation

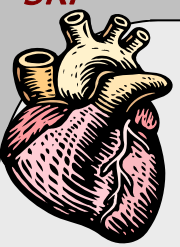
- HTA or systematic review conclusions regarding economic studies
- Economic analyses performed in HTAs
- New economic studies



Key Question 3
Summary of HTA findings

Prior HTA/SR reviewed a total of 43 economic studies

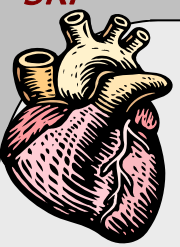
- Median QHES score (19 studies; 2 reviews' critique) = 62
  (scale 0 - 100)
- ICER for DES per each QALY gained:
  $27,540 (USD) - €1,099,858
- ICER for DES per revascularization avoided:
  $1,650 - $ 7,000 (USD)
- ICERs most influenced by:
  - price premium for DES, # stents per procedure and revascularization rates



Key Question 3- new studies
Cost effectiveness of DES vs. BMS

New Studies: 4 HTA's own, one additional

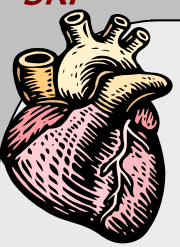
- Median QHES score = 94 (range 86-100)
- ICER for DES per each QALY gained:
  €40,467 – over €1 million
- ICER for DES per revascularization avoided:
  $2,630 (CAN$) - €4,974
- ICERs influenced by price premium of DES, #stents per procedure, revascularization rates



Key Question 3
Cost effectiveness of DES vs. BMS

Conclusions

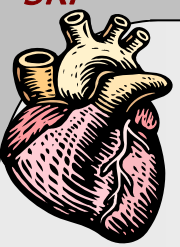
- Great variability across studies in assumptions and parameters used
- Common themes in conclusions:
  - DES not cost effective across populations
  - Evidence suggests DES may be cost effective in selected higher risk patients with multiple risk factors
- Most recent analyses conducted outside US
- Quality of life measures received limited attention in the studies reviewed
- Studies did not project beyond 2 year time horizon



Key Question 3- new studies
Cost effectiveness of DES vs. BMS

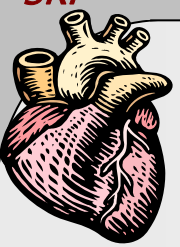
Methodologically rigorous full economic studies using US data and system parameters are needed. Studies should include:

- Health status or quality of life measures at important points along clinical pathway
- US-based event probabilities and absolute rates
- Costs that reflect current costs, best practice and reimbursement policies in the US that are appropriate for the perspective taken.



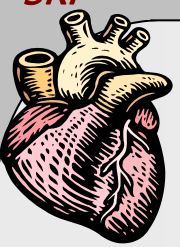
Key Question 1- **Efficacy and Effectiveness Summary**

- **Overall strength evidence (SoE):**
  - **Efficacy SoE is High**
    - Neither DES or BMS are favored with respect to mortality, cardiac mortality or myocardial infarction based on conventional MA and follow-up to 4 years
    - DES are favored with regard to TLR
  - **Effectiveness SoE is Low**
    - There are mixed results; it is unclear whether DES or BMS are favored with regard to mortality, cardiac mortality and myocardial infarction in studies with >1 year follow-up
    - DES are favored with regard to TLR



Key Question 2 – **Safety Summary**

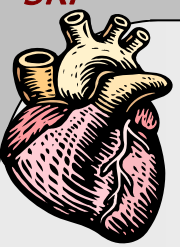
- **Stent thrombosis- SoE is Moderate**
  - Most HTAs and recent meta-analysis indicate no significant difference in stent thrombosis and late stent thrombosis between DES and BMS
  - Studies, including MAs, may be underpowered for evaluation of stent thrombosis overall and late stent thrombosis in particular
- **Other outcomes- SoE is very low**
  - Case series for bleeding and stent fracture only



Key Question 3 – **Economic analyses Summary**

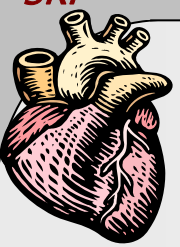
Overall strength of evidence: Low

- HTA reviews of 43 economic studies + 5 additional analyses suggested DES not cost effective across populations vs. BMS but may be in special populations
- Broad range of outcomes and ICERs
- Significant variability in modeling, quality and consistency of findings
- Methodologically rigorous US-based study needed



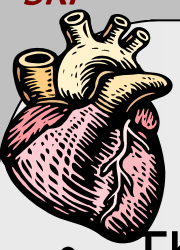
Diabetic patients
Summary

- Diabetic patients - Efficacy
  - No differences in mortality, cardiac death or MI in those with ≥ 6 months DAT (0 to 4 years);
  - 2-fold increase in mortality and cardiac death in those with < 6 months (0 to 4 years)
    - **Strength of evidence is moderate**
  - Significant reduction in TLR with DES
    - **Strength of evidence is high**



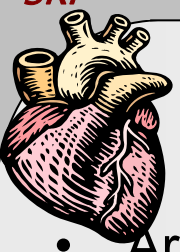
Diabetic patients
Summary

- Diabetic patients – Effectiveness
  - Mixed results for death/cardiac death, no difference in MI
    - **Strength of evidence is very low**
  - TLR less frequent with DES
    - **Strength of evidence is low**
- Diabetic patients - Safety
  - Although no differences between DES and BMS for stent thrombosis or late stent thrombosis were found, there may be insufficient power to detect a difference
    - **Strength of evidence is low**



HTA Report interpretation: What we know

- There is no statistically significant difference between DES and BMS with regard to death, cardiac death or myocardial infarction up to 4 years.
- DES are consistently associated with lower rates of TLR
- While no statistically significant differences in stent thrombosis or late stent thrombosis were seen, analyses may be underpowered; no comparative studies for bleeding
- Among diabetic patients, < 6 months of dual anti-platelet therapy was associated with a 2-fold increase in death and cardiac death with DES but there was no difference in MI regardless of therapy duration
- Nonrandomized studies show mixed results for death and MI
- Most extensive CEAs concluded DES were not cost-effective in general populations; ICERs driven by DES cost, #,TLR
- Professional guidelines do not address use of DES vs. BMS



Remaining Questions

- Are statistically significant findings also clinically significant? Are the risk differences of public health importance?
- How should the relative importance of the various outcomes be weighed, over the short-term and over the long-term?
- Is TLR/TVR correlated with decreased rates of death, cardiac death and MI over the long term? Why or why not?
- How might newer DES designs or drugs compare with BMS for various outcomes in the short term and long term?
- What is the long term safety of prolonged anti-platelet use?
- What are the specific indications for DES vs. BMS in general and special populations? What are the indications for TLR?
- Will methodologically rigorous US-based CEAs draw different conclusions from HTA CEAs as ICERs are driven by DES cost, number of stents and TLR?
- How does comparison of DES vs. BMS fit within the bigger context of comparative effectiveness with medical therapy, CABG and other treatments?


Questions?

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on these questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are Evidence based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards. [2]

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms.[3]

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

Using Evidence as the basis for a Coverage Decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of Evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the Evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- the amount of evidence (sparse to many number of evidence or events or individuals studied);
- consistency of evidence (results vary or largely similar);
- recency (timeliness of information);
- directness of evidence (link between technology and outcome);
- relevance of evidence (applicability to agency program and clients);
- bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. Factors for Consideration - Importance

At the end of discussion at vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- risk of event occurring;
- the degree of harm associated with risk;
- the number of risks; the burden of the condition;
- burden untreated or treated with alternatives;
- the importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- the degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- value variation based on patient preference.

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

Medicare Coverage and Guidelines

Organization	Date	Outcome	Evidence Cited?	Grade / Rating
Medicare Pub. 100-03 WA-HTA report P.42	NR	No national coverage decision (NCD) specific to bare metal versus drug eluting stents. Overall PTA coverage memo: PTA (with and without the placement of a stent) is covered when used in accordance with FDA approved protocols for treatment of atherosclerotic lesions of a single coronary artery for patients for whom the likely alternative treatment is coronary bypass surgery and who exhibit the following characteristics: (1) angina refractory to optimal medical management; (2) objective evidence of myocardial ischemia; and (3) lesions amenable to angioplasty. Coverage for all other indications is at local Medicare contractor discretion.	No	N/A
Guidelines – WA HTA p. 41 and App. N	NA	No guidelines for clinical care or appropriateness have been published regarding the use of BMS versus DES. Most comprehensive joint ACC/AHA guidelines address broader perspective on setting and issues involved in the decisions leading to coronary stent placement.		

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document: What are the key factors and health outcomes and what evidence is there?

Safety Outcomes	Safety Evidence
Mortality - Overall Mortality	
Morbidity - Stent Thrombosis - Early - Late	
- Bleeding	
- Stent Fracture	
Efficacy/Effectiveness Outcomes	**Efficacy/Effectiveness Evidence**
Freedom from Cardiac mortality	
Freedom from MI	
Freedom or reduction of TVR/TLR	
Cost Outcomes	**Cost Evidence**
Other Factors	**Evidence**
Special Populations	

Clinical Committee Evidence Votes

First voting question
The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Is there sufficient evidence under some or all situations that the technology is:

	Unproven (no)	**Equivalent** (yes)	**Less** (yes)	**More** (yes)
Effective				
Safe				
Cost-effective				

Discussion
Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second vote
Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not Covered. _____ Covered Unconditionally. _____Covered Under Certain Conditions.

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Clinical Committee Findings and Decisions

Next Step: Cover or No Cover
If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions
If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Efficacy Considerations:

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
    - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
    - Adverse effect on health that can result in lasting harm or can be life-threatening.
- Other morbidity concerns
- Short term or direct complication versus long term complications
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?