Clinical End Points in Coronary Stent Trials
A Case for Standardized Definitions

Donald E. Cutlip, MD; Stephan Windecker, MD; Roxana Mehran, MD; Ashley Boam, MSBE; David J. Cohen, MD; Gerrit-Anne van Es, PhD, MSc; P. Gabriel Steg, MD; Marie-angèle Morel, BSc; Laura Mauri, MD, MSc; Pascal Vranckx, MD; Eugene McFadden, MD; Alexandra Lansky, MD; Martial Hamon, MD; Mitchell W. Krucoff, MD; Patrick W. Serruys, MD; on behalf of the Academic Research Consortium

Background—Although most clinical trials of coronary stents have measured nominally identical safety and effectiveness end points, differences in definitions and timing of assessment have created confusion in interpretation.

Methods and Results—The Academic Research Consortium is an informal collaboration between academic research organizations in the United States and Europe. Two meetings, in Washington, DC, in January 2006 and in Dublin, Ireland, in June 2006, sponsored by the Academic Research Consortium and including representatives of the US Food and Drug Administration and all device manufacturers who were working with the Food and Drug Administration on drug-eluting stent clinical trial programs, were focused on consensus end point definitions for drug-eluting stent evaluations. The effort was pursued with the objective to establish consistency among end point definitions and provide consensus recommendations. On the basis of considerations from historical legacy to key pathophysiological mechanisms and relevance to clinical interpretability, criteria for assessment of death, myocardial infarction, repeat revascularization, and stent thrombosis were developed. The broadly based consensus end point definitions in this document may be usefully applied or recognized for regulatory and clinical trial purposes.

Conclusion—Although consensus criteria will inevitably include certain arbitrary features, consensus criteria for clinical end points provide consistency across studies that can facilitate the evaluation of safety and effectiveness of these devices. (Circulation. 2007;115:2344-2351.)

Key Words: restenosis • stents • thrombosis • clinical trials

Clinical trials designed to evaluate the safety and effectiveness of drug-eluting coronary stents (DES) play pivotal roles in both new device approval and in their adoption for clinical use. Although surrogate markers may have some role in the definition of device performance, direct measures of clinical outcomes are preferable in the understanding of the response of human subjects’ exposure to these combination drug–device products.¹

The selected end points must serve several purposes. They must have both short- and long-term pathophysiological relevance to device performance, they must represent clinically meaningful events, and they must be sufficiently defined, preferably through blinded processes, to be subjected to statistical analysis. Because of the intrinsic limitations in the ability to obtain histology, serial examinations, or other mechanistic detail from human subjects, clinical end points for DES studies are bound to include certain arbitrary assumptions and will frequently vary across clinical trials as the result of different approaches to such assumptions. Variability in end point definitions, however, creates a formidable barrier to the understanding of results across clinical trials or the pooling of results for the detection of rare safety signals.

With the recognition that consistency across well-considered end point definitions is critical to this process, 4 academic research organizations involved in the design and management of current DES clinical trials combined efforts in an informal collaboration termed the Academic Research Consortium (ARC) to orchestrate a set of consensus definitions for DES study end points. Two meetings that also...
included representatives of the US Food and Drug Administration (FDA) and device manufacturers that worked at the time with the FDA on DES clinical trial programs were held in Washington, DC, in January 2006 and in Dublin, Ireland, in June 2006 (see the online-only Data Supplement). The charge for the consortium was to select appropriate individual clinical end points, define the criteria to determine the occurrence of the end point, and consider the potential to group individual end points into meaningful composites of both device-oriented and patient-oriented outcomes. Importantly, the mission of this first ARC effort was to achieve well-considered consensus definitions without detailing per se all aspects of how these definitions should be applied for trial designs or other related analyses.

General Criteria for DES Clinical End Point Definitions

Three general criteria were considered for each end point definition. First, the end point definitions should support the characterization of device effectiveness or safety. In the following discussion, it is the ARC consensus that safety end points represent any adverse outcome whether specifically related to the use of the device or not, and effectiveness end points refer specifically to maintenance of coronary artery luminal patency. Second, the end point definitions should relate to the pathophysiological mechanism(s) most likely responsible for the clinical outcome. Finally, the proposed criteria should balance the need for consistency with the legacy of published literature against the need for adaptation of definitions based on newly emerging knowledge.

Clinical End Point Measures of Device Safety: General Considerations

DES-related safety issues are governed to some degree by time. Adverse outcomes within 30 days of implantation are generally considered temporally related to the procedure. In the setting of a progressive entity such as coronary disease, the later that adverse events occur, the more likely they are to represent an interaction between the device and the disease or to represent new disease activity altogether.

Event definitions may also vary in relation to the treated population. For example, periprocedural myocardial infarction (MI) or sudden death within 30 days in elective patients may clearly be device- or procedure-related, whereas in patients with acute or evolving MI such relationship may not be clear.

Clinical End Point Measures of Device Effectiveness: General Considerations

DES are implanted for the treatment of obstructive coronary artery disease. Their effectiveness is measured by the relief of such flow-limiting obstructions, initially through structural mechanisms and later with preservation of the luminal dimension through inhibition of neointimal hyperplasia or restenosis.

Effectiveness clinical end points are designed to assess clinically significant restenosis, assessed objectively as a requirement for ischemia-driven repeat revascularization, either of the stented segment itself (target lesion revascularization [TLR]) or of the stented vessel or its side branches (target vessel revascularization). Target vessel failure, proposed as any target vessel revascularization, death, or MI attributed to the target vessel, is an even broader metric of failed effectiveness and adjusts for the potential bias introduced when patients who die or sustain MI before the end of the TLR end point time are considered to be free from TLR. Ostensibly, one might also consider persistence or recurrence of angina during follow-up as evidence of failed effectiveness (because not all episodes of clinical restenosis will lead to repeat revascularization), but we believe that this end point does not lend itself as readily to objective assessment as the other proposed end points and is better measured as a stand-alone end point with the use of formal, validated health status instruments.

Patient-Oriented (Global) Cardiovascular End Points: General Considerations

The optimal basis for DES evaluation should be overall cardiovascular outcomes from the patient’s perspective, including all death, MI, and repeat revascularization procedures. These outcomes reflect the complex interplay between device performance, revascularization strategy, secondary prevention, and key patient descriptors. Both the time course and the composite selected should characterize patient well-being related to the pathophysiology of the implanted DES device and its impact on underlying coronary artery disease outcome. For example, whether a device improves functional capacity and quality of life, but does not affect MI rates or mortality—as is the case for percutaneous intervention in elective cases—should be clear so that regulatory authorities, clinicians, and reimbursement agencies can carefully weigh the net benefit against possible safety concerns.

Proposed Safety and Efficacy End Points

Death

Death that occurs after a coronary stent procedure may be clearly related to a device- or procedure-related complication, in which case the role of the device is clear. Death may also occur unexpectedly during the follow-up period, either as a result of an evident cardiac event, unexplained sudden death, or noncardiac cause. ARC considers all-cause mortality the most unbiased method to report deaths in a clinical trial or observational study, even though it may be less specific than deaths adjudicated as cardiac in origin (Table 1).

For times when attribution to cardiac versus noncardiac causes is desired, such as during long-term follow-up studies, ARC proposes a conservative approach (Table 1). Specifically, all deaths are considered cardiac unless an unequivocal noncardiac cause can be established. Cardiac deaths should include all events related to a cardiac diagnosis, a complication of the procedure, treatment for a complication of the procedure, or an unexplained cause. Unexpected death even in patients with coexisting and potentially fatal noncardiac disease (eg, cancer, infection) should be classified as cardiac unless history related to the noncardiac diagnosis suggests death was imminent. Mortality should then be reported as all-cause as well as cardiac mortality versus noncardiac. It
### TABLE 1. Classifications of Death

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>Any death due to proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), witnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death.</td>
</tr>
<tr>
<td>Vascular death</td>
<td>Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.</td>
</tr>
</tbody>
</table>

All deaths are considered cardiac unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal noncardiac disease (eg, cancer, infection) should be classified as cardiac.

May also be desirable to subcategorize noncardiac death by vascular versus nonvascular causes.

### Myocardial Infarction

MI during a clinical trial of a percutaneous coronary intervention (PCI) device may occur during the immediate periprocedural period as a result of the index study procedure or long after the procedure, as a result of spontaneous MI or late complications of the study device or subsequent revascularization procedures. Even the most recent DES clinical trials have relied on older modified World Health Organization criteria to establish the diagnosis of MI, with threshold values of total creatine kinase ≥2 times the upper limit of normal rather than more sensitive and specific biomarkers. Furthermore, these definitions have not included more variable thresholds to distinguish periprocedural from spontaneous MI. Representatives of the European Society of Cardiology and the American College of Cardiology have provided recommendations to redefine diagnostic criteria for MI and together with the American Heart Association and World Heart Federation have recently updated these guidelines to call for a universal definition for clinical as well as investigational trial use. In its most recent document, this global task force strongly encourages clinical trialists to adopt the proposed definitions for consistent application across investigational studies (Tables 2 and 3).

After careful consideration, the ARC agrees with this added level of consensus and proposes a classification system that is consistent with the global task force recommendation and highlights areas that require additional consideration. The global task force recommends the establishment of criteria based on troponin or creatine kinase Mb (CKMB) but notes the preference for troponin in all cases. For either troponin or CKMB, the upper range limit is defined as the 99th percentile of the normal range. The periprocedural period includes the first 48 hours after PCI and first 72 hours after coronary artery bypass grafting (CABG).

### Periprocedural MI After PCI

For periprocedural MI after PCI, it is important to distinguish events defined by a threshold level of enzyme or biomarker elevation where the degree of elevation has a proven relationship to other more meaningful clinical outcomes. Although the global task force notes the absence of solid scientific evidence for the establishment of such a threshold, they have recommended a value >3 times the upper range limit. Several investigators have reported correlation of elevated CKMB of >3, >5, or >8 times normal with increased mortality, but there has been reluctance to use troponin in this setting because of concerns over its extreme sensitivity as a measure. In 1 study, many more patients reached the threshold of >3 times the normal range for troponin than for CKMB (22% versus 4%). Although even minimally elevated troponin has been associated with increased late mor-

### TABLE 2. Myocardial Infarction Classification and Criteria for Diagnosis*

<table>
<thead>
<tr>
<th>Classification</th>
<th>Biomarker Criteria†</th>
<th>Additional Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periprocedural PCI</td>
<td>Troponin &gt;3 times URL or CKMB &gt;3 times URL</td>
<td>Baseline value &lt;URL</td>
</tr>
<tr>
<td>Periprocedural CABG</td>
<td>Troponin &gt;5 times URL or CKMB &gt;5 times URL</td>
<td>Baseline value &lt;URL and any of the following: new pathologic Q waves† or LBBB, new native or graft vessel occlusion, imaging evidence of loss of viable myocardium</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>Troponin &gt;URL or CKMB &gt;URL</td>
<td>Symptoms suggestive of ischemia and any of the following: new ST elevation or LBBB, documented thrombus by angiography or autopsy</td>
</tr>
<tr>
<td>Sudden death</td>
<td>Death before biomarkers obtained or before expected to be elevated</td>
<td>If biomarkers increasing or peak not reached then insufficient data to diagnose recurrent MI</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>Stable or decreasing values on 2 samples and 20% increase 3 to 6 hours after second sample</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Global Task Force. URL indicates upper reference limit, defined as 99th percentile of normal reference range; LBBB, left bundle-branch block; and ST, stent thrombosis.
†Baseline biomarker value required before study procedure and presumes a typical rise and fall.
‡Q waves may be defined according to the Global Task Force, Minnesota code, or Novacode.
CKMB elevations studies have reported associations of adverse outcome and studies where CABG is compared with DES. Although follow-up in PCI trials or at the time of the index treatment in The diagnosis of MI after CABG may be an issue during may prefer the use of total creatine kinase or CKMB definitions in cases where historical comparisons are critical, but in these cases we encourage CKMB rather than total creatine kinase.

**Periprocedural MI After CABG**

The diagnosis of MI after CABG may be an issue during follow-up in PCI trials or at the time of the index treatment in studies where CABG is compared with DES. Although studies have reported associations of adverse outcome and CKMB elevations >5, >10, or >20 times the upper rate limit, the interpretation of isolated biomarker elevation after CABG is difficult because several sources of such elevation can be anticipated, including cardiac manipulation, ventricular venting, and suture placement. The ARC concurs with the global task force that biomarker elevation alone is inadequate for the diagnosis of periprocedural MI after CABG and accepts the proposed definition of troponin or CKMB >5 times the upper rate limit when associated with new pathological Q waves or left bundle-branch block, angiographically documented new graft or native vessel occlusion, or imaging evidence of new loss of viable myocardium.

**Spontaneous MI**

MI after the periprocedural period may be secondary to late stent complications or progression of native disease. Performance of ECG and angiography supports adjudication to either a target or nontarget vessel in most cases.

With the unique issues and pathophysiological mechanisms associated with these later events as well as the documented adverse impact on short- and long-term prognosis, the ARC proposes a more sensitive definition than for periprocedural MI and supports the global task force criterion of any elevation of troponin above the upper range limit. For the purposes of evaluation of results of PCI clinical trials, we do not find it useful to distinguish spontaneous events caused by acute coronary ischemic events from those related to increased demand or other causes for decreased supply as proposed by the task force, and we will consider all late events that are not associated with a revascularization procedure simply as spontaneous.

**Special Situations**

The global task force addresses other specific situations that are applicable to the diagnosis of MI in PCI clinical trials. The importance of baseline biomarkers is highlighted to exclude elevation before the index procedure. Recurrent MI or reinfarction may be diagnosed when biomarker levels are stable on 2 samples that are >6 hours apart or are in decline if a subsequent value 3 to 6 hours after the procedure is increased by ≥20% from the baseline sample. If the baseline value is not stable, then insufficient data exist to recommend biomarker criteria for diagnosis, and the ARC recommends that these events be considered as preprocedure MI. The global task force also addresses the role of ECG for diagnosis of MI. Pathological Q waves are defined according to amplitude, location, and depth if present in at least 2 contiguous leads; other classifications, such as Minnesota code and Novacode, are also acceptable for diagnosis. The presence of Q waves as defined may be used to diagnose interval or prior MI and have also been used to subclassify periprocedural and spontaneous MI as Q wave or non–Q wave. ECG interpretation by a blinded core laboratory is recommended. Finally, the global task force addresses patients who suffer sudden death before biomarker data can be obtained or before the appearance of cardiac biomarkers in the blood. In the presence of supporting data, such as ischemic symptoms, new ST-segment elevation, new ST-segment elevation, or reinfarction may be diagnosed.

**Repeat Revascularization**

Assessment of Clinical Effectiveness, Reduction of Restenosis

Clear and consistent definition of TLR is crucial to the understanding of variations in DES effectiveness, whether across different patient populations, lesion categories, or the devices themselves. Criteria for TLR should define procedures that are performed for clinically significant renarrowing and thus include 2 fundamental components: the luminal measurement and the clinical context. Luminal narrowing provides anatomic evidence of device performance failure. The clinical status of the patient provides a more direct reflection of the clinical outcome associated with an ineffective device-based intervention. The ARC definition requires symptoms or functional evidence of ischemia as well as lesion severity of >50% diameter stenosis determined by an independent quantitative coronary angiographic core laboratory (Table 4).

The ARC recommendation extends to encouraging DES study designs to require completion of clinical evaluations at a point in time before any protocol catheterization, intra-vascular ultrasound, or other imaging. Implicit to this approach is that all interval catheterizations, and hence all TLRs that take place during the clinical evaluation window, will de facto be clinically driven.

Several studies have confirmed the bias of increased TLR events introduced by protocol catheterization. With this
comes the dilemma of whether patients would have remained stable for a long time without further revascularization or would soon have become symptomatic if revascularization had not been performed. Although attempts have been made to stratify TLR driven by protocol catheterization, even independent adjudication is very complex in this setting.2 Thus, the ARC consensus for DES evaluation is to primarily assess clinically driven TLR within a time interval that precedes any protocol-mandated repeat catheterization and include subsequent TLR in secondary analyses, with best adjudication as to clinical need. We suggest determination of TLR at 12 months with protocol follow-up angiography at 13 months.

Early TLR events (before 30 days) also require special consideration. The pathophysiology is more likely to be caused by an angiographic complication, because this time course is too short for fibrointimal hyperplasia, which is the more likely mechanism after 30 days.19,20 The ARC consensus is that TLR before 30 days is a safety end point and not a measure of restenosis, whereas TLR after 30 days is a measure of failed DES effectiveness.

**Composite End Points**

Composites generated by the combination of individual end points provide additional statistical power to detect potentially meaningful differences between treatments. The individual components should each represent clinically meaningful events and should be linked by common elements of pathophysiology. Composite acronyms such as MACE (major adverse cardiac event) have been used so frequently with so many variations in definition that ARC recommends that the term be avoided altogether (Table 5).

### Table 4. Repeat Revascularization

| Target lesion revascularization | TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLRS should be classified prospectively as clinically indicated* or not clinically indicated by the investigator prior to repeat angiography. An independent angiographic core laboratory should verify that the severity of percent diameter stenosis meets requirements for clinical indication and will overrule in cases where investigator reports are in agreement. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent. |
| Target vessel Revascularization | TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself. |

TLR indicates target lesion revascularization; TVR, target vessel revascularization; and QCA, quantitative coronary angiographic.

* A revascularization is considered clinically indicated if angiography at follow-up shows a percent diameter stenosis ≥50% (core lab QCA assessment) and if one of the following occurs: (1) a positive history of recurrent angina pectoris, presumably related to the target vessel; (2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; (3) abnormal results of any invasive functional diagnostic test (eg, Doppler flow velocity reserve, fractional flow reserve); (4) A TLR or TVR with a diameter stenosis ≥70% even in the absence of the above-mentioned ischemic signs or symptoms.

The ARC consensus suggests 2 composite end points for DES trials, one that is device-oriented and one for overall patient-oriented clinical outcome. The device-oriented composite includes cardiac death, MI attributed to the target vessel, and TLR. The broader patient-oriented outcome composite includes all-cause mortality, any MI, and any revascularization (includes TLR), target vessel revascularization, or revascularization of nontarget vessels.

Other composites, such as a net clinical benefit that may include safety-related events such as bleeding or stroke, might have application for specific clinical trials. The ARC consensus for DES end points was to recognize such events as secondary safety end points.

**Stent Thrombosis**

Stent thrombosis is a rare but usually catastrophic event, frequently associated with large MI or death.21,22 In the bare metal stent clinical trials of mostly noncomplex lesions, stent thrombosis rates were <1% with the use of dual antiplatelet therapy and high-pressure postdilation,21 although higher rates (2% to 3%) were reported when more complex patients and lesions were treated.23 Almost all events occurred within the first few days and were not reported after 30 days by definition. In fact, it was not until late thrombosis events were recognized with increasing frequency during early brachytherapy clinical trials that reports of late thrombosis after bare metal stents appeared.24–27 Initial reports of DES clinical trials showed no increased risk for stent thrombosis during 1- and 2-year follow-up compared with bare metal stents,5,6,28 but concerns have been heightened recently by reports of increased risk beyond the recommended dual antiplatelet therapy period,29 continued risk beyond 2 years in real-world patients,30 and pooled or meta-analysis of published studies that showed increased mortality or MI for sirolimus DES compared with bare metal stents (Tables 6 and 7).31,32

The sensitivity and specificity of definitions of stent thrombosis will vary depending on whether the evidence required is more conservative or more expansive. In previous DES and bare metal studies, stent thrombosis definitions have ranged from requiring evidence of acute myocardial ischemia with angiographic confirmation of thrombus or unexplained sudden death within 30 days5,6,21,33 to including MI that involves the target vessel territory6,21,22,34,35 or unexplained
cardiac deaths regardless of timing as representative of at least possible or presumed stent thrombosis.22,35

The ARC consensus is that both levels of evidence and timing of events can be stratified to define varying degrees of certainty and to imply different pathophysiological mechanisms, respectively. The trilevel of certainty classification recommended is shown in Table 7.

Definite stent thrombosis classification requires angiographic or autopsy confirmation, is highly specific, and is patterned on the definition developed when these events were first detected during early brachytherapy clinical trials.37,38 Although it maximizes specificity, the definite classification may not be sufficiently sensitive for the capture of a relatively rare safety event. The categories of probable and possible stent thrombosis add such sensitivity, but the utility of these categories will vary depending on the quality of data available to the adjudication committee. This is particularly true for the least specific thrombosis category, possible, which could be assigned to all late deaths unless sufficient detail is provided for adjudication. It is important to avoid the dilution of a potential real difference in events with the use of an overly sensitive definition that may include cases unlikely to represent thrombosis. The ARC recommends the combination of adjudicated definite and probable stent thrombosis to best characterize this aspect of DES safety; however, the reporting of definite only and overall rates is also encouraged.

In addition to the level of certainty, stent thrombosis should be stratified relative to the timing of the event. The ARC consensus recommends temporal categories of early (0 to 30 days), late (31 days to 1 year), and very late (>1 year after implantation). Early stent thrombosis (0 to 30 days) will be used in the remainder of this document.

TABLE 6. Stent Thrombosis: Timing

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute stent thrombosis*</td>
<td>0 to 24 hours after stent implantation</td>
</tr>
<tr>
<td>Subacute stent thrombosis*</td>
<td>&gt;24 hours to 30 days after stent implantation</td>
</tr>
<tr>
<td>Late stent thrombosis†</td>
<td>&gt;30 days to 1 year after stent implantation</td>
</tr>
<tr>
<td>Very late stent thrombosis†</td>
<td>&gt;1 year after stent implantation</td>
</tr>
</tbody>
</table>

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheter laboratory.

*Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30 days) will be used in the remainder of this document.

†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

TABLE 7. Definite,* Probable, and Possible Stent Thrombosis

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite stent thrombosis</td>
<td>Angiographic confirmation of stent thrombosis†</td>
</tr>
<tr>
<td></td>
<td>The presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and present in at least 1 of the following criteria within a 48-hour time window:</td>
</tr>
<tr>
<td></td>
<td>Acute onset of ischemic symptoms at rest</td>
</tr>
<tr>
<td></td>
<td>New ischemic ECG changes that suggest acute ischemia</td>
</tr>
<tr>
<td></td>
<td>Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)</td>
</tr>
<tr>
<td></td>
<td>Nonocclusive thrombus</td>
</tr>
<tr>
<td></td>
<td>Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.</td>
</tr>
<tr>
<td></td>
<td>Occlusive thrombus</td>
</tr>
<tr>
<td></td>
<td>TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).</td>
</tr>
<tr>
<td>Pathological confirmation of stent thrombosis</td>
<td>Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.</td>
</tr>
<tr>
<td>Probable stent thrombosis</td>
<td>Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:</td>
</tr>
<tr>
<td></td>
<td>Any unexplained death within the first 30 days§</td>
</tr>
<tr>
<td></td>
<td>Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause</td>
</tr>
<tr>
<td>Possible stent thrombosis</td>
<td>Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.</td>
</tr>
</tbody>
</table>

*Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.
†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).
§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

of clopidogrel discontinuation and without clear relationship to the usual technical or lesion risk factors.41,42 Furthermore, events continue to occur at similar rates up to 3 years.30 Histopathological evaluations have suggested idiosyncratic hypersensitivity and persistent inflammatory changes with delayed or absent stent strut endothelialization as possible mechanisms for this ongoing risk.43,44

Reporting of late or very late stent thrombosis may be complex to interpret when events occur secondary to an intervening TLR, especially if an additional or different stent is implanted at that time. Censorship of all such events, however, may bias reporting in favor of devices with higher restenosis risk. The ARC consensus recommends reporting of
all stent thrombosis events, with secondary reporting of primary (no intervening TLR) stent thrombosis. It should be noted that the ARC definitions require evidence of a clinical event and do not include silent late occlusions as manifestations of stent thrombosis. It is our opinion that, although these clinically silent events may represent thrombosis, they more likely represent a gradual renarrowing caused by severe restenosis.

Conclusion

The DES represents an exciting area of breakthrough technology, which has generated an enormous literature in parallel with widespread use in a short period of time. Interaction of innovative stent platforms, polymers, and molecular entities, as well as pharmaceutical adjuncts such as dual antiplatelet therapy, present a unique degree of complexity for systematic ongoing evaluation of these devices, their optimal use, and their real safety and performance results.

Toward this end, clinical trials and DES industry programs have developed a broad variety of end point definitions, which differ across a heterogeneous array of arbitrary cut-off values, timing of end point assessment, and outcome composites that are nominally the same but are inconsistent in terms of individual components and in the mixing of device- and patient-oriented outcomes.

The ARC was created as an informal orchestration of academics, clinical trialists, the FDA, and DES device manufacturers grounded in the recognition that consistency of end point definitions across the DES literature would contribute far more than would the application or abandonment of any particular arbitrary cut-off values. The process combined available mechanistic and outcomes data with clinical and logistical perspectives to consider what end point definitions would be most informative for DES performance evaluation (pivotal) studies. The primary deliverable was not intended to outline study requirements or practice standards, but rather to communicate the consensus definitions and a brief context of their rationale as a point of reference for manufacturers, trialists, clinicians, and regulatory authorities. Although consensus for DES trials was the impetus for our effort, the definitions are likely applicable to trials of any PCI device.

The final document is by nature dynamic, but modifications should follow a similar mechanism for consensus. In principle, the consensus calls for recognition of the importance of standard reporting of specific device-related clinical events of death, MI, TLR, and stent thrombosis and the net impact of device treatment on overall clinical outcome assessed by all-cause mortality, MI, and repeat revascularization procedures. Use of central core laboratories and independent, blinded, end point adjudication is central to standardization of the definitions. In this manner, the balance of device risk and benefit can best be assessed for clinical trial subjects and future individual patients.

Limitations

This informal consensus document and the ARC end point definitions have a number of limitations. First, the clinical trial end point definitions proposed are not easily supported by scientific evidence as single gold standards, but represent reasonable options that are based on available data. Second, attempts to evaluate previous clinical trials through retrospective application of these definitions and readjudication of events should be undertaken with caution and for the generation of hypotheses only, given the potential for bias relative to prospectively defined end points. Finally, it must be recognized that, although broadly based consensus definitions are an important step in the right direction, how these definitions are actually applied in specific clinical trials for specific DES investigations is not fully addressed in this first ARC effort.

Sources of Funding

Grants were provided to Harvard Clinical Research Institute and Cardialysis to cover costs of travel, meeting rooms, and lodging for academic attendees at the Washington, DC, and Dublin meetings by Abbott Vascular, Biosensors International, Boston Scientific Corporation, Conor Medsystems, Cordis Corporation, Guidant, and Medtronic.

Disclosures

None.

References


Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions
Donald E. Cutlip, Stephan Windecker, Roxana Mehran, Ashley Boam, David J. Cohen, Gerrit-Anne van Es, P. Gabriel Steg, Marie-angèle Morel, Laura Mauri, Pascal Vranckx, Eugene McFadden, Alexandra Lansky, Martial Hamon, Mitchell W. Krucoff and Patrick W. Serruys on behalf of the Academic Research Consortium

Circulation. 2007;115:2344-2351
doi: 10.1161/CIRCULATIONAHA.106.685313

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/115/17/2344

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2007/04/25/115.17.2344.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/