Percutaneous coronary intervention has become the most frequently used method of myocardial revascularization. The advent of coronary stenting led to a significant decrease in the complications seen after balloon angioplasty, resulting in improved patient outcome. Yet, stented angioplasty has been plagued from the onset by early stent thrombosis (<30 days after index procedure) and late in-stent restenosis (ISR). Initially, stent thrombosis rates as high as 24% raised serious doubts as to the viability of the therapy. With the combined prescription of thienopyridines and aspirin for 4 to 8 weeks, together with proper stent deployment techniques, early stent thrombosis rates decreased to what was felt to be an unavoidable and acceptable 1% to 1.5%. At the same time, efforts to reduce the 30% late ISR rates through systemic pharmacological approaches remained unsuccessful until local radiation, a strong antiproliferative therapy, was applied to prevent or treat ISR. Vascular brachytherapy was the first illustration that delayed healing might portend an increased risk of thrombosis together with the expected reduction in restenosis. Indeed, stent thrombosis rates increased again up to 5.3%, and the time window of event occurrence was extended beyond 1 year so that the initial clinical benefit would eventually erode as time went by. Today, first-generation drug-eluting stents (gen1-DES: Cypher, Cordis, Johnson & Johnson, Miami Lakes, Fla [sirolimus-eluting stent, SES] and Taxus, Boston Scientific Corp, Natick, Mass [paclitaxel-eluting stent]) releasing an antiproliferative compound (sirolimus or paclitaxel, respectively) via a nonbioerodable polymer have been proved to reduce the incidence of ISR by up to 75%. Since the publication in 2002 of the first randomized trial comparing DES and bare metal stents (BMS) in highly selected patients and lesions, the use of DES in clinical practice has expanded to the majority of coronary lesion subsets (eg, de novo complex lesions, long lesions, small vessels), to high-risk patients (multivessel angioplasty, patients with diabetes mellitus), and more recently, to primary percutaneous coronary intervention for ST-segment elevation acute myocardial infarction (MI). From the literature, Cypher and Taxus appear to yield similar rates of repeat revascularization, although some studies suggest that the luminal preservation achieved by the Cypher stent and measured by coronary angiography may be slightly superior to that of the Taxus stent. Late stent thrombosis (LST; >30 days after index procedure), although rare, is again emerging as a cause for concern with both types of gen1-DES.

Response by Serruys and Daemen p 1455
Understanding the pathophysiology of late thrombosis of gen1-DES seems essential for assessing the clinical relevance of these unpredictable and potentially lethal events. On the basis of the evidence that is available from preclinical, autopsy,
and clinical studies, we propose that the pathophysiological
evergies known as Virchow’s triad may be responsible for
LST with gen1-DES.53 Furthermore, we comment on the clinical
evidence derived from industry-sponsored and investigator-
driven trials that suggests a small but relevant incremental risk of
LST with gen1-DES compared with BMS.

Delayed Vascular Healing as a Consequence
of Gen1-DES Implantation

Autopsy studies have shown that after BMS deployment an
inflammatory reaction takes places in the vessel wall that
involves macrophages and T lymphocytes with few B lymphocytes and giant cells.54–56 After implantation of gen1-
DES, a more pronounced inflammatory response has been
described that may occasionally be associated with a local
hypersensitivity reaction and eosinophilic infiltration.48,50

The synthetic nonbioerodable polymer containing the drug
may be an important trigger of local coronary inflammation,48,50,57–59 even though the metal struts60 or the drug itself
may participate in this phenomenon.61 Coronary inflammation is responsible for both delayed reendothelialization of
stent and vessel wall56,62 and destruction of medial vessel wall
layers, causing positive regional remodeling, all of which
eventually result in a delayed vascular healing response.48,50

Clinically, local inflammatory response and delayed or incomplete arterial healing manifest on angiography by aneurysm formation but also can be suspected in the presence of late acquired stent malapposition (LASMA), as was observed with imaging modalities such as intravascular ultrasound (IVUS),63–66 Incomplete strut apposition by IVUS (which includes both persistent malapposition and LASMA) has been observed in 21% of the patients assigned to SES in the Randomized Study With the Sirolimus-Eluting Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (RAVEL) trial.67 The incidence of LASMA was close to 10% in both the Sirolius-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS)46 (8.7%) and TAXUS II69 (8.7%) trials. According to these trials, 1 of 10 to 20 lesions with LASMA will develop an angiographically visible aneurysm.54,60 This incidence has been confirmed in the TAXUS V trial in which 1.4% of the patients developed late acquired aneurysms in the paclitaxel-eluting stent arm.38

Pathophysiology of LST

These local changes in vascular biology, in combination with
systemic alterations of coagulation pathways, are reminiscent of
the pathophysiological mechanisms described in 1856 by
Rudolf Virchow and could be responsible for LST with gen1-DES51: (1) an abnormal vessel wall lining (eg, incomplete endotherialization), (2) an abnormal blood-flow pattern (eg, slow flow), and (3) altered blood constituents (eg, increased blood thrombogenicity). Any of these elements alone or in combination favors intravascular thrombus for-
mation.53,70 This generic mechanism of disease can be applied
specifically to the coronary arteries after implantation of
gen1-DES45–49 and can be delineated as follows.

Abnormal Vessel Wall Lining

In the first month after the implantation of a BMS, a new
endothelial layer covers the stent struts, reestablishing a “normal” coronary vessel wall lining, thus reducing the risk of
LST secondary to strut or vessel surface thrombogenicity.54–56 Gen1-DES inhibit or may even abolish this physi-
ological vessel wall healing, leaving the struts in direct contact with flowing blood and blood elements.48,50,71 Complete or partial lack of reendothelialization of stent struts and vessel
wall generates a long-lasting,62 if not permanent, unhealed vessel wall surface favoring platelet adhesion and aggrega-
tion, which may eventually cause thrombus formation.48,50

With BMS, incomplete reendothelialization also has been
observed,55 but unlike the case with DES, it was not seen in
series of comparative case reports.50

Abnormal Blood-Flow Pattern

Within 8 months, the inflammatory vessel wall response to
gen1-DES implantation may induce a positive regional vascular
wall remodeling, as shown by histology48,50 or IVUS,63 may be
responsible for LASMA,57–60 or even, in extreme cases, may
cause angiographically visible aneurysm.56,64–66 These structural
changes (vessel widening) may induce, according to the law of
continuity,72 slow flow velocities and low shear stress particu-
larly in the vicinity of the stent struts73 and possibly on the
abluminal side between the stent struts and the coronary wall.
Slow flow velocity is known to promote thrombogenesis,53,72 as
demonstrated by the increased propensity for acute MI to occur
in aneurysmal-ectasic vessels74 and suggested by thrombotic
occlusion of gen1-DES at the site of aneurysmal dilatation.48,50,72
Therefore, regional positive vascular remodeling within the stent
increases the surface-related prothrombogenicity of both vessel
wall and stent struts.75

Abnormal Blood Constituents

Increased blood thrombogenicity plays a crucial role in
favoring LST. The prothrombotic effect of the reduction or
discontinuation of aspirin,76 ADP receptor inhibitors46,47 (eg, clopidogrel), or both79 may be further potentiated by an
ongoing systemic inflammatory reaction77,78 (eg, fever, post-
operative course, malignancy) or by dehydration.79

The Link Between the Antirestenosis Effect of
Gen1-DES and LST

The mechanism of the antirestenosis properties of gen1-DES is
best appreciated by detailed measurements of arterial dimen-
sions with either coronary angiography or IVUS. Late loss (LL)
is a quantitative coronary angiography parameter used to mea-
sure indirectly the inhibitory potential of DES on neointimal
formation. It is defined as the minimal luminal diameter after
the procedure minus the minimal luminal diameter at follow-up and is frequently plotted on frequency-distribution curves. From
randomized comparisons with BMS, it appears that the
Widening of the coronary lumen over time may reduce both intrastent flow velocity and wall shear stress. Segmental slow flow may be caused by a local intravascular abnormality (e.g., LASMA, aneurysm, or bifurcational stenting) and by a global coronary perfusion abnormality (e.g., diastolic coronary perfusion determined by variables such as tachycardia, increased telediastolic pressure, microangiopathy, distal embolization) and thereby give rise to prolonged interaction between vessel wall and blood constituents. Finally, abnormal blood constituents influenced by systemic factors such as dehydration, inflammation (e.g., increased fibrinogen), and hemostatic balance (e.g., anticoagulation/antiplatelet treatment) will increase intrastent thrombogenicity. Because these determinants of the risk of LST vary over time and from patient to patient, it is not surprising that LST remains largely unpredictable.

The link between the antirestenosis effect or healing response measured by LL and clinical events (LST and ISR) after gen1-DES implantation can be described as a J-shaped curve relationship: Both negative and high LL are linked to an excess in clinical events (Figure 2). LST is rare (flatter portion of the J curve) and more likely to occur in the patient population with negative LL (larger lumen by angiography as a result of delayed healing or nonhealing). Repeat revascularization is frequent (steeper portion of the J curve) and occurs more often as the LL values increase (smaller angiographic lumen as a result of exuberant healing and neointimal growth). Any increase in the population with negative LL is expected to increase the absolute number of patients potentially subject to LST (Figure 3).

Therefore, the paradigm that predicates the use of quantitative coronary angiography (or IVUS) as a surrogate end point for both efficacy and safety outcome may no longer be valid in the setting of technologies that interfere with vascular healing.

Identifying the Population at Risk for LST
To identify patients at higher risk for LST with gen1-DES and to assess the magnitude of the problem, one should focus on the local inflammatory response and delayed healing. According to quantitative coronary angiography, the proportion of cases below the 0-mm LL point, represented by the area under the negative part of the frequency-distribution curve of LL values, is close to 50% (Figure 3). According to IVUS and the incidence of LASMA, the patient population at risk for LST after gen1-DES can be estimated on average at 10% (RAVEL, 13 of 91; SIRIUS, 7 of 80; TAXUS II, 20 of 229; Diabetes and Sirolimus-Eluting Stent [DIABETES], 11 of 75; total, 51 of 475 or 11%).

The fact that the shift to the left of the frequency-distribution curve of LL after SES implantation seems more pronounced in the subgroup at highest risk for ISR is noteworthy. The mean in-segment LL is −0.02 mm in
patients with insulin-dependent diabetes mellitus versus 0.09 mm in patients with non–insulin-dependent diabetes, as opposed to 0.56 versus 0.42 mm after BMS implantation. Therefore, this subset of patients at higher risk of ISR also is more likely to develop incomplete healing and positive remodeling.86 The fact that LASMA secondary to gen1-DES is more frequent in patients with an increased risk of restenosis seems counterintuitive because some degree of resistance to the antiproliferative action of DES would be expected in patient/lesion subtypes with higher propensity for ISR.85,86 However, this observation has recently been confirmed by serial IVUS analyses in diabetic patients in whom LASMA was observed in 14.7% of the cases after SES compared with 0% after BMS implantation ($P<0.001$).85

**Recognizing LST**

Assessing the true incidence of rare safety-related events such as LST is not trivial. One can focus on the potential clinical consequences of the event (eg, death and nonfatal MI) or on the event itself using angiographic or pathological evidence of stent thrombosis. The clinical end points are less specific for LST but more sensitive than angiographic assessment and will thus achieve a more “inclusive” recognition of LST. Reporting only the LST event itself may appear more specific but represents a less sensitive and a definition-dependent approach that pictures a more “restrictive” recognition, with the potential for underestimation. When dealing with safety issues, we can make a case for using broad and inclusive assessment methods. These methodological issues complicate the assessment of LST. Rates of death and MI may be affected by potential confounding factors during the process of “adjudication to prespecified event definitions” or by “partial reporting,” leading to an underestimation of clinically serious events. Predefined adjudication of events such as cardiac and noncardiac death and Q-wave and non–Q-wave MI is almost systematically used in gen1-DES trial programs.15–39 Event adjudication is particularly problematic for death (ie, cardiac or noncardiac death) because sudden-onset cardiac events in patients with cancer or intercurrent infection may truly be related to stent thrombosis and yet adjudicated as noncardiac. Indeed, prothrombotic changes (eg, inflammatory status, dehydration) in patients with advanced noncardiac disease (eg, malignancies) may trigger cardiac death. Of interest is the fact that in the Cypher clinical program15–27 all-cause death was reported, whereas in the Taxus program,28–39 mortality events were restricted to adjudicated cardiac death (except for TAXUS V, VI [oral presentation at 2 years], and the pilot trial TAXUS F38,39–39) (Tables 1 through 4). Overall in the Cypher and Taxus randomized trials, mortality rates were higher in the gen1-DES arm compared with the BMS arm (4.67% versus 3.33% and 2.15% versus 2.01%; Tables 1 through 4). The lower absolute mortality rate in the Taxus versus the Cypher trial programs (2.15% versus 4.67%) may simply be related to the adjudication process. Thus, it would seem advisable to report both all-cause death and adjudicated cardiac death. Of note, in

*Figure 2. J-curve relationship between LL and clinical events. A negative LL (left part of the curve) and an increasing positive LL (right part of the curve) are both linked to more clinical events. Events such as late thrombosis are more likely to occur in the population with a negative LL (left arm of the curve), and events such as restenosis are more likely to occur with progressively increasing LL (right arm of the curve). Modified from Camenzind,82 with permission of the publisher. Copyright © 2006, the Massachusetts Medical Society.*
randomized trials, serious events (death and MI) were more common in the Taxus than the Cypher group.42–45

When stent thrombosis events are reported with the more specific approach, the use of predetermined definitions has proved to be problematic. Early stent thrombosis is defined as an ischemic event up to 30 days after the index procedure, an event which can include unexplained death, Q-wave MI, or (sub)abrupt closure requiring revascularization. In contrast, LST is defined as ischemic event/H11022 30 days after the index procedure that includes solely MI attributable to the target vessel with angiographic documentation of thrombus or total occlusion at the target site and freedom from an interim revascularization of the target vessel (so-called late angiographic stent thrombosis [LAST]). Thus, unlike the case with early stent thrombosis, the definition of LAST does not take into account all potential clinical presentations of stent thrombosis by excluding death and even ECG-documented Q-wave MI in the absence of angiography. Requiring angiographic documentation of intracoronary thrombosis assumes that direct percutaneous coronary intervention will be used universally to treat acute MI patients, which is far from being the case. Instead, with reperfusion after successful thrombolysis and antithrombotic therapy, the diagnosis of LAST may be dismissed, even when delayed angiography is available. Using this restrictive definition likely underestimates the true rate of LST and smooths out differences between devices over short observation periods.87 Recognizing these issues, a proposal has been put forward to categorize stent thrombosis (Dublin or ARC definitions) according to timing (acute, subacute, late, and very late) and level of documentation (definite, probable, and possible), which illustrates that LST is highly dependent on definition and adjudication (D.E. Cutlip, personal communication, September, 2006). This “unifying” definition improves the comparability across trials but will not necessarily guarantee a more accurate assessment of the incidence of LST with gen1-DES. An example is that including stent thromboses that follow interim revascularization of the target vessel has a major impact on LST rates (excluded according to study protocol definitions). As a result, thrombosis events that are consecutive to the treatment of ISR in the control arm (eg, with in-stent implantation of gen1-DES or brachytherapy) may counterbalance the spontaneously occurring LST in the gen1-DES arm. Finally, because of the small sample size of many of these trials, even a small number of patients excluded from analysis (eg, because of lost to follow-up, revoked patient consent, or follow-up out of the predefined time-window) may have a large impact on comparative outcomes. These methodological issues illustrate the complexities entailed by the analysis, presentation, and comparison of such trials and databases.

Assessing the Safety of Gen1-DES: From LST to All-Cause Mortality

Although we recognize the limitations in our ability to detect rare side effects and the difficulties in comparing the different studies, we have attempted to evaluate the relative safety profile of gen1-DES and BMS from the analysis of the following events: all-cause mortality, with and without excluded patients, per protocol and per intention-to-treat analysis (Tables 5 and 6) and LST as the target safety event, defined in a pathogenetically pertinent and clinically relevant manner (Tables 1 through 4). All official data sources have been consulted and compared to verify data consistency.15–39 The following data sources were retained: (1) published peer-reviewed articles, (2) presentations at major meetings (American College of Cardiology, American Heart Association, European Society of Cardiology, Euro–Paris Course on Revascularization, and Transcatheter Cardiovascular Therapeutics), (3) printed information distributed by the industry, and (4) latest updated data on file from the industry. It is important to realize that practice guidelines prepared by
scientific societies are using solely peer-reviewed articles as data sources. The additional data sources were included to increase the analysis sample and to capture the longest available follow-up period. Indeed, it is unusual when the peer-reviewed publication appears within 1 year after the official first presentation, and follow-up presentations are frequently not published.

The most appropriate manner to assess safety is under debate. A more rigorous approach to assess safety to maximize the detection of rare adverse events, at least in device trials in which compliance is not really a confounding factor, seems to be the use of as-treated analysis (better option) or per-protocol analysis. On the contrary, a more rigorous approach to assess efficacy is an intention-to-treat analysis.

An inclusive approach to mortality is to use calculated mortality defined as the sum of all-cause mortality plus the excluded patients, assuming that their death is a worst-case hypothesis (Tables 5 and 6). For the Cypher program, a per-protocol analysis was not performed, and the number of patients excluded from the intention-to-treat analysis were

| TABLE 1. Serious Adverse Events in Cypher Versus BMS Trial Program According to Intention-to-Treat Analysis |
|-----------------------------------------------|---------|---------|---------|---------|---------|---------|
|                                               | S C     | S C     | S C     | S C     | S C     | S C     |
| RAVEL; S, n=120; C, n=118                     |         |         |         |         |         |         |
| Death–all, n                                  | 0 2     | 2 2     | 6 3     | 9 5     | 13 7    |         |
| Death–c, n                                    | ND ND   | ND ND   | ND ND   | ND ND   | ND ND   | 3 5     |
| Q-MI, n (alternate data)                      | 2 0     | 2 1 (0) | 2 0     | 3 2     | 3 1     |         |
| Death–all and Q-MI, n (alternate data)        | 2 2     | 4 3 (2) | 8 3     | 12 7    | 16 8    |         |
| SIRIUS; S, n=533; C, n=525                    |         |         |         |         |         |         |
| Death–all, n                                  | 5 7     | 7 4     | 11 7    | 21 15   |         |         |
| Death–c, n                                    | ND ND   | 3 2     | 4 3     | ND ND   |         |         |
| Q-MI, n (alternate data)                      | 4 2     | 4 2     | 6 (5)   | 5 (3)   | 7 3     |         |
| Death–all and Q-MI, n (alternate data)        | 9 5     | 11 6    | 17 (16) | 12 (10) | 28 18   |         |
| E-SIRIUS; S, n=175; C, n=177                  |         |         |         |         |         |         |
| Death–all, n                                  | 2 1     | ND ND   | 4 5     | 7 7     |         |         |
| Death–c, n                                    | ND ND   | ND ND   | ND ND   | ND ND   |         |         |
| Q-MI, n                                       | 2 0     | ND ND   | 3 0     | 4 1     |         |         |
| Death–all and Q-MI, n                         | 4 1     | ND ND   | 7 5     | 11 8    |         |         |
| C-SIRIUS; S, n=50; C, n=50                    |         |         |         |         |         |         |
| Death–all, n                                  | 0 0     | ND ND   | ND ND   | ND ND   |         |         |
| Death–c, n                                    | ND ND   | ND ND   | ND ND   | ND ND   |         |         |
| Q-MI, n                                       | 0 0     | ND ND   | ND ND   | ND ND   |         |         |
| Death–all and Q-MI, n                         | 0 0     |         |         |         |         |         |

S indicates sirolimus (Cypher); C, control; death–all, all-cause mortality (in Cypher program, always all-cause mortality reported); death–c, adjudicated cardiac death; Q-MI, Q-wave MI; and ND, no data available.

Data for RAVEL 7-month follow-up and 1-year follow-up are taken from Morice et al; 2-year follow-up, Morice et al; 3-year follow-up, Morice et al; and 4-year follow-up, Sousa et al. Data for SIRIUS 9-month follow-up are taken from Moses et al; 1-year and 2-year follow-up, Weisz et al; and 3-year follow-up, Leon et al. Data for E-SIRIUS 9-month follow-up are taken from Schofer et al; and 2- and 3-year follow-up, Legrand et al. Data for C-SIRIUS 9-month follow-up are taken from Schampert et al.

For references 15, 17, 18, 19, 20, 23, 24, and 26, see http://www.theheart.org/article/765395.do.

By guest on November 9, 2017 http://circ.ahajournals.org/ Downloaded from
kindly provided on request (Table 5; D. Donohoe, data on file, Cordis). Focusing on the intention-to-treat patient population, calculated mortality presents as a 2-times-lower risk difference (0.72% versus 1.34%) compared with all-cause mortality when evaluating the Cypher arm and the BMS arm (Table 5). The same comparison in the Taxus program using the more rigorous per-protocol population showed a 2-times-higher risk difference (0.85% versus 0.31%) in the calculated compared with the all-cause mortality (Table 6; J. Koeglin, data on file, Boston Scientific). These results may be interpreted in the following manner: The intention-to-treat population of the Cypher program may not only level out but also invert the gradient between calculated and all-cause mortality. Conversely, the higher gradient in calculated mortality versus all-cause mortality in the Taxus program may reflect both the use of the per-
have scrutinized. As shown in Tables 7 and 8, it is of major concern is the variability of the reported all-cause mortality according to the different sources that we have on the global safety assessment. The potential impact that the collection of excluded patients could have on the global safety assessment.

Tables 7 and 8 show all-cause mortality rates according to different data sources for the Cypher and Taxus trial programs. Of major concern is the variability of the reported all-cause mortality according to the different sources that we have scrutinized. As shown in Tables 7 and 8, it is of particular concern that all-cause mortality rates appear to differ between published peer-reviewed literature and data on file at the companies, especially when the latter are lower than the former. The biggest limitation in comparing these data derives from the fact that all-cause mortality is not systematically reported (e.g., adjudicated cardiac mortality is reported instead). Further subtle differences in data reporting may be encountered (e.g., results are reported as percentages but without mention of the excluded patients, precluding calculation of the absolute number of events).

To assess LST in a clinically relevant manner, definitions should be respectful of the mechanism of disease leading to the event. Most appropriately, LST should be defined in the same way as acute thrombosis (<30 days). For the time period >30 days after the index procedure, death and MI are the most frequently encountered clinical presentations of LST. However, non–ST-segment elevation MI generally is secondary to revascularization procedures, mainly as a result of the treatment of ISR (see case narratives for the Cypher and Taxus program when available). Accordingly, the incidence of the combined serious events (all-cause death and Q-wave MI) up to the latest available follow-up time point was 60% higher in the Cypher than in the BMS group (6.26% versus 3.91%; Table 2), suggesting a prothrombotic effect of gen1-DES. The risk was consistently higher throughout all available clinical follow-up time points (6 to 9 months, 1 year, 2 years, 3 years) with >15% of total death and >95% of Q-wave MI in the gen1-DES group, a finding that suggests that the increased risk persists up to 3 years (Tables 9 and 10).

Accordingly, the incidence of stent thrombosis can be estimated to range from ~2% per year (according to the follow-up of the combined data of RAVEL, SIRIUS, and E-SIRIUS up to 3 years) to 3.4% per year (according to the follow-up data up to 4 years of RAVEL solely) compared with 1.34% and 1.07% per year after randomization to BMS in the Cypher and Taxus programs, respectively (Tables 9 through 11). A similarly consistent gradient of risk, albeit of

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### TABLE 4. Serious Adverse Events in the Taxus Versus BMS Trial Program According to Intention-to-Treat Analysis, Pooled Trials Up to Latest Follow-Up

<table>
<thead>
<tr>
<th>Event Type</th>
<th>PT, (N=1670): Events, n (% of Patients)</th>
<th>C, (N=1688): Events, n (% of Patients)</th>
<th>ΔPT−C: ΔEvents, n (Risk Difference, %)</th>
<th>(Risk Difference)/Control Risk: Relative Risk Difference, %</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death−all</td>
<td>36 (2.15) 34 (2.01) 2 (0.14) 7 0.79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q-MI</td>
<td>19 (1.13) 14 (0.83) 5 (0.3) 36 0.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death−total and Q-MI</td>
<td>55 (3.28) 48 (2.84) 7 (0.44) 15 0.46</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1 and 3. Percentages are given with respect to patient at follow-up time point.

*According to χ² test.

### TABLE 5. Calculated Death and All-Cause Mortality in the Cypher Versus BMS Trial Programs Up to Latest Available Follow-Up in Intention-to-Treat Patients According to Data on File at Cordis

<table>
<thead>
<tr>
<th>Event Type</th>
<th>S (N=878): Events, n (% of Patients)</th>
<th>C (N=870): Events, n (% of Patients)</th>
<th>ΔS−C: ΔEvents, n (Risk Difference, %)</th>
<th>(Risk Difference)/Control Risk: Relative Risk Difference, %</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient excluded*</td>
<td>40 (4.56)</td>
<td>45 (5.17)</td>
<td>−5 (−0.61)</td>
<td>−12</td>
<td></td>
</tr>
<tr>
<td>Death−all</td>
<td>41 (4.67) 29 (3.33) 12 (1.34) 40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death−calculated*</td>
<td>81 (9.23) 74 (8.51) 7 (0.72) 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Death−calculated indicates the sum of death−all and excluded patients. Other abbreviations as in Table 1.

*According to intention-to-treat analysis and data on file at Cordis on October 6, 2006 (no per-protocol analysis available).
From independent registries75,95 of unrestricted use of gen1-DES, the rate of LAST (the restrictive definition of LST) was 0.17% to 0.35% per year (incidence calculated as LAST over the mean follow-up), which also reflects a 2- to 3-times-higher incidence than with BMS (0.1% per year). Finally, an analysis of pooled data from 2 high-volume institutions (the ThoraxCentre, Rotterdam, the Netherlands, and University Hospital, Bern, Switzerland), representing >8000 patients treated with gen1-DES, has suggested that the risk of LAST may accrue at a steady rate of ≈0.6% per year, with no indication that event curves are reaching a plateau at up to 3 years.96 These findings from real-life practice that include up to 60% off-label use of the devices are in agreement with the present analysis, which is restricted to the data reported from randomized clinical trials15-39 (Tables 9 through 11).

**Clinical Implications**

Administration of dual antiplatelet therapy, usually maintained for 3 to 6 months after gen1-DES deployment, generally can counterbalance the increased thrombogenicity favored by delayed vessel healing and local inflammation.16,21,25,27,28,31,36,38 The importance of dual antiplatelet therapy is underscored by the finding that its interruption appears to be the single most potent correlate of LST,46,47,49,51,92 with an impressive hazard ratio of 163 (95% CI, 26 to 998; P<0.001).99 This phenomenon had already been observed when stenting was associated with brachytherapy.97-99 In addition, in the BASKET-late analysis, thrombosis-related events occurred between 15 and 362 days after discontinuation of clopidogrel,94 indicating that intercurrent events that interfere with blood thrombogenicity may still trigger LST. Thus, the excess risk of LST may not be confined to the days after clopidogrel discontinuation.77-79 The 2005 European Society of Cardiology and the 2005 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions recommendations88,89 suggest maintaining dual antiplatelet therapy for 12 months, at least “in patients who are not at high risk of bleeding.” Given the relation between discontinuation of dual antiplatelet therapy and LST, clinicians may be tempted to continue such therapy even longer. However, the extent to which protracted dual antiplatelet therapy with aspirin and clopidogrel confers protection against LST is unknown, although such therapy was shown to portend genuine bleeding risks, as demonstrated in the Management of Atherothrombosis With Clopidogrel in High-Risk Patients With TIA or Stroke (MATCH) and Clopidogrel for High Athero-

**TABLE 6. Calculated Death and All-Cause Mortality in the Taxus Versus BMS Trial Programs Up to Latest Available Follow-Up in Per-Protocol Patients According to Data on File at Boston Scientific**

<table>
<thead>
<tr>
<th>Patients excluded*</th>
<th>PT (N=1733)*: Events, n (% of Patients)</th>
<th>C (N=1744)*: Events, n (% of Patients)</th>
<th>∆PT-C: Events, n (Risk Difference, %)</th>
<th>(Risk Difference)/Control Risk: Relative Risk Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death—all*</td>
<td>64 (3.69)</td>
<td>55 (3.15)</td>
<td>9 (0.54)</td>
<td>17</td>
</tr>
<tr>
<td>Death—all*</td>
<td>60 (3.46)</td>
<td>55 (3.15)</td>
<td>5 (0.31)</td>
<td>10</td>
</tr>
<tr>
<td>Death calculated*</td>
<td>124 (7.16)</td>
<td>110 (6.31)</td>
<td>14 (0.85)</td>
<td>14</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1, 3, and 5. Percentages are given after correction for “excluded patients” at follow-up time-point.

*According to per-protocol analysis and data on file at Boston Scientific on September 15, 2006.

**TABLE 7. All-Cause Mortality in the Cypher Versus BMS Trial Program According to Different Data Sources**

<table>
<thead>
<tr>
<th>Death—all, n</th>
<th>S C</th>
<th>S C</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL; S, n=120; C, n=118</td>
<td>Death—allo</td>
<td>6 3 9 5</td>
</tr>
<tr>
<td>and Morice et al 19 (3 years)*</td>
<td>Morris et al 19 (3 years)*</td>
<td>ND ND 9 5</td>
</tr>
<tr>
<td>Holmes et al 19†</td>
<td>Data on file</td>
<td>6 3 9 6</td>
</tr>
<tr>
<td>SIRIUS; S, n=533; C, n=525</td>
<td>Death—all, n</td>
<td>11 7 21 15</td>
</tr>
<tr>
<td>Moses 20 (2 years) and Leon et al 21 (3 years)*</td>
<td>Weisz et al 22 and Holmes et al 22†</td>
<td>11 7 21 17</td>
</tr>
<tr>
<td>Data on file</td>
<td>11 8 21 16</td>
<td></td>
</tr>
<tr>
<td>E-SIRIUS; S, n=175; C, n=177</td>
<td>Death—all, n</td>
<td>4 5</td>
</tr>
<tr>
<td>Legrand et al 23*</td>
<td>Nordman et al 23†</td>
<td>4 5</td>
</tr>
<tr>
<td>Holmes et al 23†</td>
<td>Data on file</td>
<td>5 6</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Data on file at Cordis on October 6, 2006.

*Presentation.
†Article.
thrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trials,\textsuperscript{100,101} and carries significant costs that may render very long-term prescription unpractical or inaccessible to many patients. Even in the short-term, the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) study has shown that up to 14% of patients will not be compliant with the prescribed dual antiplatelet therapy for a variety of reasons.\textsuperscript{92} In addition, when noncardiac surgical, dental, or biopsy procedures—all intercurrent events frequently occurring in the adult patient population treated with percutaneous coronary intervention and even more so in elderly with multiple comorbidities—are contemplated, difficult dilemmas arise as to the most appropriate clinical management strategy.

Instead of prolonging the duration of dual antiplatelet therapy in all patients, it would be more helpful to be able to identify subgroups of patients at higher risk of LST in relation to an increased incidence of delayed or nonhealing vascular response after implantation of gen1-DES. Invasive surrogate markers such as negative LL by quantitative coronary angiography or LASMA by IVUS are helpful for understanding mechanisms but cannot be used to screen all patients.

At the same time, it is acknowledged that continuing interaction exists between gen1-DES and the vessel wall, resulting in dynamic changes in size of plaque and vessel dimensions, for at least 2 years after implantation.\textsuperscript{102} Therefore, quantitative coronary angiography or IVUS obtained at a single time point (eg, 6 to 9 months) may not be predictive for the long term in the individual lesion/patient. Among the potential clinical predictors, the available data suggest that patients with diabetes mellitus appear to be at higher risk of LST perhaps for longer periods of time. Another group of patients at higher risk are those with overlapping gen1-DES.\textsuperscript{103} Multivariable analysis of pooled databases that include individual patient data would be most helpful in determining which patient groups may benefit most from treatment with gen1-DES and those in whom the risk of LST, and its potentially catastrophic consequences, is unacceptable high.

Given the current concerns about the long-term safety of gen1-DES and the uncertainties about the potential duration of the incremental risk, the indiscriminate daily use of gen1-DES implantation in all patients undergoing percutaneous coronary intervention no longer seems advisable. In patients at low risk for ISR or in patients at high risk for LST, the clinical benefit in terms of ISR reduction may be offset by an increased risk of LST, which carries significant morbidity and mortality.\textsuperscript{51} Therefore, when gen1-DES are preferred over BMS, physicians and patients may be trading relatively benign events such as restenosis and repeat revascularization for a rare but potentially fatal event caused by stent thrombosis. These undeniable safety concerns should not be viewed as detracting from the benefit of stented angioplasty with DES but rather as a reminder of the need to accumulate large data sets with long-term follow-up to identify subgroups with balanced safety and efficacy outcome, as well as additional information on the optimal duration of antiplatelet therapy.

**TABLE 8.** All-Cause Mortality in the Taxus Versus BMS Trial Program According to Different Data Sources

<table>
<thead>
<tr>
<th></th>
<th>9 Months</th>
<th></th>
<th>1 Year</th>
<th></th>
<th>2 Years</th>
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<th>3 Years</th>
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<tbody>
<tr>
<td></td>
<td>PT C</td>
<td>PT C</td>
<td>PT C</td>
<td>PT C</td>
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<td>PT C</td>
<td>PT C</td>
<td>PT C</td>
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<tr>
<td>TAXUS I; PT, n=31; C, n=30</td>
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<td></td>
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<tr>
<td>n</td>
<td>30</td>
<td>30</td>
<td>27</td>
<td>28</td>
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<tr>
<td>Death–all, n‡</td>
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<td></td>
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</tr>
<tr>
<td>Grube et al\textsuperscript{28} and Grube et al\textsuperscript{29}†</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
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<td>Data on file</td>
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<tr>
<td>TAXUS V; PT, n=577; C, n=579</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>n</td>
<td>560</td>
<td>567</td>
<td>556</td>
<td>563</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Death–all, n</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ellis\textsuperscript{37}*</td>
<td>ND</td>
<td>ND</td>
<td>12</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stone et al\textsuperscript{36}†</td>
<td>7</td>
<td>8</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
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<td>Data on file</td>
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<tr>
<td>TAXUS VI; PT, n=219; C, n=227</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n</td>
<td>216</td>
<td>219</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death–all, n§</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grube et al\textsuperscript{39}†</td>
<td>1</td>
<td>5</td>
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<tr>
<td>Data on file</td>
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</tbody>
</table>

Abbreviations as in Tables 1 and 6. Data on file at Boston Scientific on September 15, 2006.

*Presentation.
†Article.
‡No presentation data available.
§No article data available.
These concerns should also be put into context. Given the relatively small total population with late follow-up available from randomized trials and the low rate of the events, there remains considerable uncertainty about the true rates of LAST with DES and BMS in real-life practice. It remains possible that the (small) risk of LAST with DES may be

### TABLE 9. Global Serious Adverse Events in the Cypher Versus BMS Trial Program (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS) Stratified by Time Point of Follow-Up (Data According to Maximal Difference $S-C$ Reported in the Literature or at Official Meetings*)

![](image)

### TABLE 10. Global Serious Adverse Events in the Cypher Versus BMS Trial Program (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS) Stratified by Time Point of Follow-Up (Data According to Minimal Difference $S-C$ Reported in the Literature or at Official Meetings*)

![](image)
offset by the clinical benefits derived from reduced need for repeat revascularizations.104

Research and Regulatory Implications

The observed safety issues are inherent to the mechanisms of action of gen1-DES, and in the future, every new DES will have to be analyzed not only by angiographic metrics but also in a clinically pertinent manner. The vascular healing response to any new device or treatment modality is the pivotal mechanism that will determine its long-term safety.82 Therefore, more focus should be placed on this issue during preclinical testing, which thus far was concentrating primarily on efficacy metrics.82 Specific experimental animal settings should be developed to better understand and test the antihealing or prohealing properties of newer-generation DES.105 The translation from preclinical studies to clinical testing and evaluation should initially be performed in small pilot trials to determine the healing response in human atherosclerotic vessels and therefore provide some indication as to the propensity for LST and hence the desirable duration of dual antiplatelet therapy. To visualize and quantify vessel healing response, sophisticated imaging methods and functional testing may prove useful when used alone or in combination (eg, angiography, IVUS, optical coherence tomographic imaging, angioscopy, in vivo studies of endothelial function). After assessment and confirmation of the vascular healing response, adequately sized clinical trials should be performed to determine clinical benefit and to confirm safety. When a new device is approved for clinical use, long-term monitoring of safety outcomes should be mandated by regulatory agencies, monitoring that should include device traceability. As is obvious from recent history, it is particularly important that adjudication of events, data monitoring, management, and analysis, as well as long-term follow-up, be performed independently from sponsoring device companies. It is important to monitor clinical safety events (such as all-cause mortality) and not solely definition-dependent and adjudication-dependent events, the incidence of which may be reduced by the use of stringent definitions. Furthermore, it is worrisome to see new DES no longer tested for superiority against BMS but rather for noninferiority with approved devices in relatively small trials and with angiographic end points. As a result, potential small increases in death and nonfatal MI rates may become part of the “background” event rate in both study arms and no longer be noticeable.

Summary

Several lines of evidence converge in suggesting that the use of gen1-DES is associated with a small but incremental risk of potential LST. Three years ago, occasional case reports alerted us to the potential for very LST (beyond 1 year) after gen1-DES placement.6,47,49 Although rare, these events bear severe clinical consequences with case-fatality rates as high as 45%.51 LST

<table>
<thead>
<tr>
<th>TABLE 11. Global Serious Adverse Events in the Taxus Versus BMS Trials (TAXUS I, II, IV, V, and VI) Stratified by Time Point of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT: Events, n ( % of Patients)</td>
</tr>
<tr>
<td>Follow-up to 6–9 mo: TAXUS I, II, IV, V, VI</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Death–total</td>
</tr>
<tr>
<td>Q-MI</td>
</tr>
<tr>
<td>Death–total and Q-MI</td>
</tr>
<tr>
<td>Follow-up to 1 y: TAXUS I, II, IV, V, VI</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Death–total</td>
</tr>
<tr>
<td>Q-MI</td>
</tr>
<tr>
<td>Death–total and Q-MI</td>
</tr>
<tr>
<td>Follow-up to 2 y: TAXUS I, II, IV, and VI</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Death–total</td>
</tr>
<tr>
<td>Q-MI</td>
</tr>
<tr>
<td>Death–total and Q-MI</td>
</tr>
<tr>
<td>Follow-up to 3 y: TAXUS I, II, IV</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Death–total</td>
</tr>
<tr>
<td>Q-MI</td>
</tr>
<tr>
<td>Death–total and Q-MI</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Total death was defined as death–c or death–all according to available data; if both were available, death–all was selected. Percentages are given with respect to patients at follow-up time point.
appears to be temporally related in part to discontinuation of antiplatelet therapy.48,52 Because most LST events occur outside hospitals, angiographic or autopsy documentation of definite stent thrombosis is often missing, with the potential for underestimation of the problem. Because of their clinical presentation, death and MI have been suggested as the ultimate clinical outcome and benchmark for LST. A critical review and pooled analysis of the available randomized clinical trial data comparing Cypher or Taxus with BMS show a consistent trend toward more frequent death and Q-wave MI at late follow-up with gen1-DES. These findings are consistent with a recently published meta-analysis106 and with the results of the BASKET-late trial94 showing a 3- to 4-fold increase in late deaths or MI. The analysis of pooled registries from 2 high-volume institutions has suggested that the risk of LAST may accrue steadily without plateauing for up to 3 years.99 Taken together, these data provide cause for serious concern about the long-term safety of gen1-DES, particularly given the size of the global population that is potentially exposed (nearly 6 million gen1-DES are already implanted worldwide). It appears that the relevance of altered vascular healing with incomplete vessel wall and stent reendothelialization and regional positive remodeling has not been fully recognized. Research efforts should focus on developing site-specific treatment modalities that combine antirestenotic and prohealing properties, allow vascular healing, and preserve late patient safety. Large trials powered for clinical outcomes, including death and nonfatal MI, are direly needed to ensure that the frequent but rather benign restenosis has not been exchanged for the rare but unpredictable and potentially lethal LST. In the meanwhile, concerns for patient safety should remain the primary guide for decision making and caution against indiscriminate use of gen1-DES.107,108

Acknowledgments

We are indebted to Dr David DeMeets and Dr Tom Cook for their critical review and suggestions, to Nicolas Masson for his precious technical support in preparing the figures, and to Dr Pierre-André Dorsaz for expert statistical support.

Disclosures

None.

References


Response to Camenzind et al

Patrick W. Serruys, MD, PhD; Joost Daemen, MD

First, let us congratulate the authors of “A Cause of Concern” for their lucid, thorough, and intelligent review of the literature suggesting that the available randomized clinical trials comparing Cypher or Taxus with bare metal stents show a consistent trend toward more frequent death and Q-wave myocardial infarction at late follow-up. Their initial presentation at the European Society of Cardiology meeting served as a wake-up call for the Food and Drug Administration felt obliged to call for a 2-day panel to assess publicly the issues raised during this particular congress. Unfortunately, the 3 authors were not present to reiterate in a regulatory forum their astute argument, which may have influenced the course of the debate on day 1. On that first day, the members of the panel, including prominent and critical noninvasive cardiologists, unanimously rejected the notion of increased risk for death and myocardial infarction for on-label drug-eluting stent use but recognized, as we did, the risk of late stent thrombosis. On day 2, the panel agreed that “the risk of death, myocardial infarction, and stent thrombosis is higher when drug-eluting stents are used off-label as compared with on-label usage, a caution that also holds true for bare metal stents, several panel members noted.” In that respect, Swedish researchers had a major impact on the panel by presenting the off-label data of their registry. We could not have agreed more when the authors of “A Cause of Concern” concluded that “long-term monitoring of safety outcome, including device traceability, should be mandated by regulatory agencies whenever a device is allowed for clinical use” and that “it is of particular importance that adjudication of events, data monitoring, management, and analysis, as well as long-term follow-up, be performed independently from sponsoring device companies.” However, our concern is that the testing of possible remedies to the current deficiencies of the first-generation drug-eluting stents will be paradoxically hindered by stringent regulatory measures as a penalty for the late recognition of their inherent limitations.
A Cause for Concern
Edoardo Camenzind, P. Gabriel Steg and William Wijns

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