National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Off-label use of coronary drug-eluting stents

Occurrence, safety and effectiveness in 'real world' clinical practice

RIVM report 360050024/2011

B. Roszek | R. de Water | J.W.G.A. Pot |
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Colofon

B. Roszek[1]
R. de Water[1,2]
J.W.G.A. Pot[1]
R.T. van Domburg[3]
R.E. Geertsma[1]

Contact:
B. Roszek
Centre for Biological Medicines and Medical Technology
boris.roszek@rivm.nl

[1] Centre for Biological Medicines and Medical Technology, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
[2] Presently Medicines Evaluation Board, The Hague, The Netherlands
[3] Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands

This investigation has been performed by order and for the account of the Dutch Health Care Inspectorate, within the framework of V/360050 'Supporting the Health Care Inspectorate on Medical Technology'

Abstract

Off-label use of coronary drug-eluting stents – Occurrence, safety and effectiveness in 'real world' clinical practice

Use of coronary drug-eluting stents (DES) for purposes other than their indications for use (off-label use) may push such devices beyond their design limits and thus potentially lead to increased risks. On the other hand, such use can be clinically relevant, treatment regimes may become a medically recognised standard and off-label use may be important for further innovation.

Worldwide, the use of DES in patients with off-label characteristics is common in clinical practice, with frequencies varying from 47% to 81% of all patients. Off-label use of DES in one large Dutch cardiovascular centre was estimated to be 68% in 2002. At a Dutch national level, no data could be found.

Promising results of DES for on-label indications have led to the application of DES in more complex situations such as multiple lesions, lesions at bifurcations, and diabetes. In some cases, this is the only treatment option available.

For unrestricted use of DES (covering off-label as well as on-label indications), there are no conclusive data from individual observational studies with regard to safety aspects compared with using a bare metal stent (BMS) for similar indications. However, in a meta-analysis by renowned investigators of observational studies and randomised clinical trials, unrestricted use of DES compared with BMS did not appear to be associated with adverse safety outcomes and was reported to be more effective. Some new-generation DES are more safe and effective when compared with first-generation DES.

Keywords:
drug-eluting stent, off-label use, unrestricted use, safety, effectiveness

Rapport in het kort

Off-label gebruik van coronaire drug-eluting stents – Vóórkomen, veiligheid en effectiviteit in 'real world' klinische praktijk

Het gebruik van drug-eluting stents (DES) voor een ander doel dan het indicatiegebied (off-label gebruik), kan leiden tot een belasting van deze hulpmiddelen buiten de grenzen van het ontwerp en mogelijk tot verhoogde risico's. Anderzijds kan een dergelijke behandelmethode klinisch relevant zijn, een medisch erkende standaard worden en kan off-label gebruik belangrijk zijn voor verdere innovatie.

Het gebruik van DES in patiënten met off-label kenmerken komt veelvuldig voor in de klinische praktijk. Gepubliceerde aantallen variëren wereldwijd tussen de 47% en 81% van alle patiënten die DES ontvangen. In één groot Nederlands cardiovasculair centrum werd off-label gebruik van DES geschat op 68% in 2002. Er werden geen gegevens op nationaal niveau in Nederland gevonden.

De veelbelovende resultaten van DES voor on-label indicaties hebben geleid tot DES toepassingen in meer complexe situaties zoals meervoudige vaatafwijkingen, vaatafwijkingen bij een vertakking en diabetes. In sommige gevallen is het gebruik van DES de enige beschikbare optie voor behandeling.

Voor onbeperkt gebruik van DES (dat zowel off-label als on-label indicaties omvat) geven individuele observationele studies geen sluitend beeld met betrekking tot veiligheidsaspecten in vergelijking met het gebruik van kale stents voor vergelijkbare indicaties. Er is echter ook een meta-analyse van observationele studies en gerandomiseerde klinische trials uitgevoerd door vooraanstaande onderzoekers. Hieruit lijkt onbeperkt gebruik van DES in vergelijking met kale stents niet te zijn geassocieerd met negatieve veiligheidsuitkomsten en wel met een hogere effectiviteit. Sommige nieuwe generatie DES zijn veiliger en hebben een hogere effectiviteit in vergelijking met de eerste generatie DES.

Trefwoorden:
drug-eluting stent, off-label gebruik, onbeperkt gebruik, veiligheid, effectiviteit

Disclosure

The authors declare that they have no conflict of interest.

This report replaces the RIVM letter report 360050020/2009 entitled ‘Off-label use of coronary drug-eluting stents’.

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Summary

After the first-generation of coronary drug-eluting stents (DES) were placed on the market, their use increased progressively in the period from 2002-2006. DES use also quickly extended beyond the populations examined in pivotal randomised clinical trials. Patients with markedly different clinical profiles and increasingly complex lesions were also treated with DES. Such procedures, which are outside the labelled indications for use, are referred to as 'off-label use'. At the 2006 European Society of Cardiology Congress, concerns sparked that patients receiving DES off-label were at higher risk of death or myocardial infarction driven by late and very late stent thrombosis. In late 2006, an advisory panel to the US Food and Drug Administration concluded that off-label use of DES was associated with increased risks based on available (sparse) data. Since 2007, numerous published studies became available, which address the safety and effectiveness of DES off-label use.

The aim of this investigation was to estimate the frequency of occurrence of off-label use of coronary DES in general and in the Netherlands in particular, to evaluate safety and effectiveness of off-label use of coronary DES, and to discuss the rationale for off-label use of DES.

A structured literature search using PubMed was performed for compiling data on frequency of occurrence, safety and effectiveness of coronary DES. Web searches were carried out for an inventory of available DES and their indications for use.

Worldwide, the use of DES in patients with off-label characteristics is common in clinical practice with frequencies varying from 47% to 81% of all patients. Off-label use of DES in one large Dutch cardiovascular centre was estimated to be 68% in 2002. At a Dutch national level, no data could be found.

For unrestricted use of DES, there are no conclusive data from individual observational studies with regard to safety aspects compared with bare metal stents (BMS) for similar indications. However, in a meta-analysis by renowned investigators of observational studies and randomised clinical trials, unrestricted use of DES compared with BMS did not appear to be associated with adverse safety outcomes and was reported to be more effective. Some new-generation DES are more safe and effective when compared with first-generation DES. Treatment regimens implying off-label use of DES are important in clinical practice, offering options to treat patients with coronary lesions. In some cases, off-label use is the only treatment option available. With growing experience, off-label use may become a medically-recognised standard of care and may be important for further innovation. Continued follow-up, especially focusing on the safety of DES in high-risk patients, is warranted in order to fully understand the long-term safety of DES.

1 Introduction

1.1 Cardiovascular diseases and their treatments

Cardiovascular diseases are among the major causes of morbidity and mortality throughout the world. In the Netherlands, cardiovascular diseases account for about 48,000 deaths per annum. Of the Dutch population (16×10^6), one million individuals have experienced symptoms of cardiovascular disease at some point in their lives. On an annual basis, well over 150,000 individuals develop a complication in relation to these diseases [Health Council of the Netherlands, 2007]. The majority of symptoms arise when coronary arteries develop a stenosis (narrowing of blood vessel), as a result of the accumulation of atheromatous plaques within the vessel tissue. This is referred to as atherosclerotic coronary artery disease. As coronary artery disease progresses, the stenosis obstructs the lumen of the artery, restricting the blood flow to the myocardium, causing myocardial ischaemia. Individuals with (near-) complete obstruction of the coronary artery typically have suffered from myocardial infarction. A rupture of the atheromatous plaque may cause an acute myocardial infarction.
In patients with severe ischaemia, coronary revascularisation aims to restore blood flow through the coronary arteries. Two well-established approaches to revascularisation for the treatment of atherosclerotic coronary artery disease are surgical myocardial revascularisation or coronary artery bypass grafting and percutaneous coronary intervention (PCI). Both methods underwent rapid development and are being refined and modified. PCI encompasses intracoronary stent implantation and balloon angioplasty (Box 1).

Box 1. Steps for catheter-based coronary interventions

A PCI procedure usually consists in accessing the femoral or radial artery using an introducer needle. A sheath introducer is placed in the opening to keep the artery open and to control bleeding. Through the sheath, a guiding catheter is pushed forward and the tip is placed at the ostium of the coronary artery. The guiding catheter allows for radio-opaque dyes to be injected into the coronary, artery allowing assessment of disease state and location using real-time X-ray imaging. Subsequently, a coronary guide wire is inserted through the guiding catheter and into the coronary artery. The wire is guided through the coronary artery to the site of the stenosis. While the guide wire is in place, a balloon catheter or other catheter-based medical device is inserted at the back of the guide wire and gently pushed forward, until the medical device is inside the stenosis.

Basically, three types of stents exist: bare metal stents (BMS), drug-eluting stents (DES) and bio-absorbable stents. DES are combination products of a medicinal substance on a polymer-free stent or embedded within a (biodegradable) polymer coating. They have been developed to solve the problem of restenosis. DES antagonise cellular reaction by local release of medication that prevents the overgrowth of scar tissue and thus reduce the need for subsequent target vessel revascularisation. Meta-analyses of randomised clinical trials showed the potential of DES in decreasing restenosis and reintervention rates compared to BMS (e.g., Babapulle et al. [2004]; Roiron et al. [2006]).
Randomised clinical trials with new DES for regulatory purposes are typically limited to studies undertaken in low-risk patients with narrow inclusion criteria. This leads to a situation where the labelling indications apply to only a minority

of patients. In an ideal world, every medical decision would be based on hard evidence but in reality, this is rarely the case. Off-label use of DES (i.e., beyond the labelled indications for use) usually occurs because on-label indications are not applicable for the majority of patients with coronary lesions necessitating medical intervention.

1.2 Safety concerns of DES

The use of DES in human atherosclerotic arteries results in disturbed vascular healing and delayed endothelialisation with uncovered stent struts as a consequence [Farb et al., 2003; Finn et al., 2007; Joner et al., 2006]. The safety of DES has been called into question because of increased susceptibility to stent thrombosis (a blood clot in the stent), a rare but serious complication. The relative impact of the stent platform, the thickness of the struts, the polymer matrix and the drug load on these processes is largely unclear [Bailey, 2009]. Hypersensitivity reactions to the polymers used in DES, delayed endothelialisation of the stents and discontinuation of dual anti-platelet therapy (combined prescription of aspirin and thienopyridines, i.e., clopidogrel or pasugrel) have all been implicated in the pathophysiology of DES thrombosis [Wernick et al., 2006]. An inherently increased thrombotic risk is likely to exist in off-label use, since it typically involves patients with more complex lesions than those represented in randomised controlled trials.
In August 2003, the French and Canadian authorities issued safety notices concerning DES, followed in September by the UK competent authority. In October 2003, the US Food and Drug Administration (FDA) announced that it had received more than 290 adverse event reports concerning stent thrombosis [Charlish, 2007]. In 2004, more clouds appeared on the horizon with a report on four patients who suffered from stent thrombosis more than eleven months after DES implantation [McFadden et al., 2004]. In an effort to better understand the risk of thrombosis, a hierarchical classification of stent thrombosis has been set by the Academic Research Consortium in 2006 (Box 2).

Box 2. Academic Research Consortium definitions of stent thrombosis

The Academic Research Consortium has put forward a proposal to categorise stent thrombosis because in most clinical trials differences in definitions and timing of clinical end points have created confusion in interpretation [Cutlip et al., 2007]. The Academic Research Consortium consensus is that both levels of evidence and timing of events can be stratified to define varying degrees of certainty and to imply different pathological mechanisms, respectively. The Academic Research Consortium recommends definite, probable and possible stent thrombosis for the levels of evidence. Definite stent thrombosis requires angiographic or autopsy confirmation and is highly specific but may not be sufficiently sensitive. The categories of probable and possible add such sensitivity but may potentially lower its specificity as the definition of stent thrombosis is expanded and includes death and myocardial infarction. The utility of these categories will vary depending on the quality of the data available. In addition to the level of certainty, temporal categories of early (0-30 days after stent implantation), late (31 days to 1 year), and very late (> 1 year) stent thrombosis can distinguish likely differences in the contribution of the various pathological processes during each of these intervals.

The real commotion about DES started at the European Society of Cardiology (ESC) Congress in September 2006. Studies were presented raising concerns about the safety of DES [Camenzind et al., 2007; Nordmann et al., 2006]. In January 2007, the FDA Advisory Panel recognised the small risk of stent thrombosis and endorsed the devices only for on-label indications (Box 3). It

was at this time that the distinction between on-label and off-label use of DES became so prominent.
Since 2007, numerous published studies have become available, which address the safety of the off-label use of DES, particularly with regard to mortality, myocardial infarction and stent thrombosis. A representative set of these studies will be discussed in this report.

Box 3. FDA Circulatory System Devices Panel meeting on DES thrombosis

On September 14, 2006, the FDA released a statement in response to inquiries asking for the agency's position on adverse events related to coronary DES. The statement noted that the FDA was aware of new data suggesting a small but significant increased risk of stent thrombosis. While the new data raised important questions, the FDA did not have enough information to draw conclusions. The FDA announced plans to convene a public panel meeting to review available data and make recommendations.
On December 7 and 8, 2006, the Circulatory System Devices Panel met in an effort to fully characterise the risks, timing and incidence of DES thrombosis [FDA, 2006a; FDA, 2006b]. The purposes of the meeting were (1) to provide a forum for the presentation of clinical data relevant to the issue of DES thrombosis (both when DES are used according to their label and in more complex patients beyond their labelled indication); and (2) to address the appropriate duration of dual anti-platelet therapy.
On January 4, 2007, FDA issued an update of the statement. The FDA Advisory Panel had the following comments and recommendations [FDA, 2007] (for a discussion see Farb and Boam [2007], Pinto Slottow and Waksman [2007] and Weisz and Stone [2008]):
▪ off-label use of DES is associated with an increased risk of death and myocardial infarction compared with on-label use of DES. One cannot exclude that stent thrombosis, especially very late stent thrombosis, is not contributing to this risk;
▪ data on off-label use of DES are limited and additional studies are needed. Data on off-label use of BMS as comparison group for off-label use of DES were not available;
▪ dual anti-platelet therapy should be continued for at least 12 months following DES PCI, especially in the off-label setting, for patients at low risk of bleeding;
▪ DES studies should have longer follow-up, enrol greater numbers of patients and include stent thrombosis as a study end point;
▪ a large randomised trial looking specifically at appropriate duration of dual anti-platelet therapy is needed;
▪ until more data become available, DES labels should state that when DES are used off-label, patient outcomes may not be as favourable as the results observed in the clinical trials conducted to support marketing approval.

1.3 Objectives and research questions

The objectives of this investigation are to study off-label use of coronary DES.

The research questions are:
a) What is the estimated frequency of occurrence of off-label use of DES in general and in the Netherlands in particular?
b) What are the safety and effectiveness of off-label use of DES?
c) Why are DES used off-label?

2 Method

2.1 Definitions

On-label use of a medical device was defined as the intended use of a medical device as indicated by the manufacturer in the instructions for use (IFU). Usually, on-label indications are based on the strict inclusion criteria for subject selection described in the clinical investigation plan (a document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation). Moreover, the IFU include contraindications and warnings and precautions describing indications that have not been clinically evaluated, usually based on the exclusion criteria for subject selection.
Off-label use of a medical device was defined as the use of a medical device for purposes other than its intended use, i.e., use in subjects with more complex clinical and anatomic presentations that were not included in the (pivotal) clinical investigation(s), which have strict enrolment criteria for patient recruitment.
Unrestricted use of a medical device was defined as the use of a medical device in an 'all-comers' patient population. Thus, unrestricted use covers both on-label indications and off-label indications. Clinical investigations with an 'all-comers' design apply wide inclusion criteria and very few exclusion criteria, which may result in a more representative sample of the target population.

2.2 DES inventory

An inventory of cardiovascular manufacturers was performed using several sources, including TCTMD on-line resource in interventional cardiology (http://www.tctmd.com), PCR Online (http://www.pcronline.com), Clinica World Medical Technology News (Informa UK Ltd, http://www.clinica.co.uk), Internet search engine Google (http://www.google.com), and the FDA database on medical device approvals (http://www.fda.gov/cdrh/pmapage.html#monthly). The inventory of DES represented an overview up to November 2011.
For CE-marked DES, manufacturers' websites were used to obtain information about medical devices, including the name of the stent and, if available, information on indication(s) for use, expansion of indications(s), date (e.g., month and year) of notified body's CE mark certification and identification of notified body (i.e., 4-digit number). Indications for use were extracted from press releases, promotional material (e.g., brochure) or IFU if downloadable from the manufacturer's web site. The FDA database was used to obtain information concerning the name of the stent, the approved indication and the date of FDA approval.

2.3 Literature search

Literature Internet searches were undertaken in PubMed (US National Library of Medicine) to identify publications with abstracts in English (last search 1 November 2011). Search terms were:

- #1 'drug-eluting stent' (6382);
- #2 'coronary artery disease' (229949);
- #3 'coronary arterial disease' (64707);
- #4 'peripheral artery disease' (18347);
- #5 'peripheral arterial disease' (57263);
- #6 'off-label use' (3279);

- #7 'unrestricted use' (5066);
- #8 'Netherlands' (258508);

The following combinations of search terms were used to narrow the search results in PubMed:

- #1 and (#2 or #3) and (#6 or #7): 90 publications;
- #1 and (#2 or #3) and (#6 or #7) and #8: 6 publications;
- #1 and (#4 or #5) and (#6 or #7): 1 publication;
- #1 and (#4 or #5): 111 publications.

No language restrictions were applied to the search strategies. Titles and abstracts were hand-searched to identify relevant publications. Randomised clinical trials of highly selected patients and lesions subgroups were not included. The identified publications were complemented by perusing reference lists of selected key publications.

2.4 Clinical evaluation of safety and effectiveness of off-label use of DES

Observational studies reporting comparative outcomes of off-label use of DES vs on-label use of DES, off-label use of DES vs off-label use of BMS, off-label use of DES vs off-label use of other DES and unrestricted use of DES vs unrestricted use of BMS were included for the analysis. In addition, studies (randomised controlled trials with 'all-comers' design and observational studies) reporting outcomes of unrestricted use of new generation DES vs first-generation DES and new generation DES vs new generation DES were included. First-generation DES release sirolimus or paclitaxel from durable polymers and stents are made of stainless steel. New generation DES are typically coated with new polymers and new medicinal substances (e.g., biolimus, everolimus or zotarolimus) and stents are made of stainless steel or cobalt-chromium alloy.
Extracted data included comparison of stent type, duration of follow-up period, and clinical outcome data. Outcomes examined were death, myocardial infarction, stent thrombosis (definite, definite/probable, late and very late stent thrombosis) and the need for reintervention of the target vessel (target vessel revascularisation). The safety and effectiveness were evaluated using the hazard ratios, odds ratios, rate ratios or relative risks and their 95% confidence intervals reported in the observational studies and randomised trials. The highest-quality estimate was extracted for the evaluation using the following rank order: propensity matched = adjusted > unadjusted.

2.5 Expert consultation

An expert in the field of interventional cardiology nominated by the Dutch Society of Cardiology (NVVC) was consulted to peer review this report.

3 Results

3.1 DES inventory

In total, 61 CE-marked DES were identified. For these CE-marked DES, publicly available information on indications for use was scarce, but different sources (web sites, press releases etc.) revealed quite diverse indications as well as different eluting medicinal substances (biolimus-A9, everolimus, novolimus, paclitaxel, simvastatin, sirolimus, tacrolimus, trapidil, tretinoin or zotarolimus). Moreover, the original indications for use of 14 DES were expanded. More information on the indications for use covered by the CE mark in Europe is shown in Table 1 (Appendix I).
Thus far, 14 DES have received FDA approval in the USA. Indications for use were less diverse and four medicinal substances are used in combination with the stent (everolimus, paclitaxel, sirolimus or zotarolimus). Since their original market approval, the indications of five DES have been expanded, i.e., DES received FDA approval for small vessel, large vessel, long lesion and/or in-stent restenosis. Although the on-label indications for use with respect to the lesion characteristics (i.e., lesion length and vessel diameter) differ among FDA-approved DES, they all included a single *de novo* lesion in native coronary artery. More information on the approved indications in the USA is shown in Table 2 (Appendix II).
Most of the current DES are designed for straight lesions and have some shortcomings when dealing with coronary bifurcation or ostial lesions. Conventional stenting techniques for these lesions require re-crossing of deployed stent struts, overlapping metal or the potential risk of incomplete coverage of the bifurcation or ostium. Therefore, easy access to the side branch and adequate coverage of the bifurcation or ostium must be taken into account. The introduction and perfection of dedicated bifurcation stents may accomplish the treatment of coronary bifurcation lesions. Recently, the paclitaxel-eluting Stentys™ Bifurcation Stent System (Stentys SAS, France), Nile Pax® Abluminal Paclitaxel Eluting Cobalt Chromium Coronary Bifurcation Stent and Nile Delta® Abluminal Paclitaxel Eluting Cobalt Chromium Bifurcation Side Branch Stent (Minvasys, France) and the AXXESS™ Biolimus A9® Eluting Coronary Bifurcation Stent System (Devax Inc, USA) have obtained the CE mark. At present, the TAXUS® Petal™ Bifurcation Paclitaxel-Eluting Stent System (Boston Scientific Corporation, USA) is undergoing clinical investigation.
For peripheral artery disease, the CYPHER SELECT™ Sirolimus-eluting Stent (Cordis Endovascular, USA) and XIENCE PRIME™ Everolimus-eluting Stent (Abbott Vascular Inc, USA) are CE-marked DES intended for the treatment of severe claudication and critical limb ischaemia in infrapopliteal (i.e., below-the-knee) lesions [PCROnline, 2011; TCTMD, 2006]. Recently, the Zilver® PTX® Drug-Eluting Peripheral Stent (Cook Medical, USA) was CE-marked for the treatment of vascular disease in femoropopliteal (i.e., above-the-knee) arteries. A still ongoing clinical investigation involves the Dynalink-E Everolimus Eluting Stent System (Abbott Vascular Inc, USA), for lesions in the superficial femoral and proximal popliteal artery.

3.2 DES applications

3.2.1 DES in coronary arteries

With restenosis significantly reduced, leading to a reduction of revascularisation procedures, the promising results with DES in carefully selected patient

populations led to the use of DES in more complex situations. These DES applications are in patients with multiple lesions, lesions at bifurcations or thrombotic lesions and in conditions such as ST-segment elevation myocardial infarction, in-stent restenosis and chronic total occlusions. For the majority of DES, these indications for use are off-label (Table 1 and 2). Off-label use of stents appears to be common in clinical practice. It is considered an important and in some cases the only treatment option available for the majority of patients with coronary lesions necessitating medical interventions.
To the best of our knowledge, publications on the frequency of occurrence of off-label use of DES at a national level in the Netherlands are not available in PubMed. However, in the Rotterdam region, interventional cardiologists at Erasmus Medical Centre and Maasstad Hospital used DES as the default strategy for every PCI immediately after the devices were launched. Moreover, observational studies have been undertaken to evaluate the safety and effectiveness of DES in unselected patients in daily practice (unrestricted use). Three 'all-comers', single centre registries have been undertaken with similar conceptual design and methodology:

- the RESEARCH registry including patients treated with the CYPHER® Sirolimus-eluting Stent (Cordis Corporation, USA) and enrolled from April 2002 up to October 2002 [Lemos et al., 2004b] with some sub-studies having extended enrolment periods (up to January 2003) in order to increase the sample size of patients [Lemos et al., 2004a];
- the T-SEARCH registry including patients treated with the TAXUS™ Express²™ or TAXUS™ Liberté™ paclitaxel-eluting stent (Boston Scientific, USA), and enrolled from February 2003 until December 2005 [Ong et al., 2005]; and
- the X-SEARCH registry including patients treated with the XIENCE™ V Everolimus-eluting Stent (Guidant Corporation, USA; currently Abbott Vascular, USA) and enrolled from March 2007 until October 2007 [Onuma et al., 2009].

In the RESEARCH registry, approximately 32% DES use was for on-label indications and in 68% DES was used for off-label indications [Serruys et al., 2005]. The major reasons for not using DES were unavailability of an appropriate stent size (i.e., diameter or length) or participation in another ongoing study.
In the RESEARCH registry, 68% of the patient population would not have been included in earlier CYPHER™ stent clinical investigations (i.e., first-in-man studies, randomised controlled trials) on the grounds that they were considered 'high risk' patients [Serruys et al., 2005]. It is assumed that a similar percentage of patients was not included in the T-SEARCH and X-SEARCH registries [unpublished data]. Major exclusion criteria for the earlier CYPHER™ clinical investigations were:

- multi-vessel stenting;
- very long lesion stenting (> 36 mm);
- ST-segment elevation myocardial infarction;
- very small vessels (stent ≤ 2.25 mm);
- bifurcation stenting;
- chronic total occlusion;
- renal impairment;
- age > 80 years;
- main stem stenting;
- saphenous vein graft stenting.

This subset of criteria closely resembles the indications for off-label use of coronary DES as defined in other investigations.

In the relatively short period of time from 2002 to 2006, DES use has reached unprecedented market share. In the early years of introduction (period 2003-2004) to the US market, 24% of the DES procedures occurred in four off-label indications (i.e., ST-segment elevation myocardial infarction, in-stent restenosis, coronary artery bypass grafting and chronic total occlusion) [Rao et al., 2006]. Other (later) studies in the USA, but also in Europe and Asia, showed that patients receiving DES for broader off-label indications ranged between approximately 47-81% [Applegate et al., 2008a; Applegate et al., 2009; Beohar et al., 2007; Brodie et al., 2008; Carlsson et al., 2009; Douglas et al., 2009; Ferreira-González et al., 2009; Flores et al., 2008; Latib et al., 2009; Lee et al., 2008; Marroquin et al., 2008; Qasim et al., 2007; Ruperto et al., 2009; Win et al., 2007; Windecker et al., 2008; Zhang et al., 2008]. However, following the turmoil at the ESC Congress in Barcelona (September 2006) and the FDA Advisory Panel statement (January 2007) DES use plummeted. For example, DES use dropped dramatically from 78% to 36% in favour of BMS in patients with ST-segment elevation myocardial infarction and off-label use in saphenous vein grafts showed a similar trend, i.e., from 74% to 43% [Gualano et al., 2010]. The clinical impact of this sharp decline is unknown.

3.2.2 DES in non-coronary arteries

The clinical successes of coronary DES in coronary arteries have inspired clinical investigators to use DES in several other arteries, both in animal studies and in clinical settings. Parts of these investigations were performed using existing coronary stents, which means their use is basically off-label. However, since the specific type of stent is often not identified in published studies and the IFU of the stents providing the indications are often not accessible, it is not clear whether some of the applied stents might be intended for additional indications and are thus not off-label. A known example is the CYPHER SELECT™ Sirolimus-eluting Coronary Stent System (Cordis Corporation, USA), for which the indication for use includes infrapopliteal lesions (see Section 3.1). In addition to this, dedicated stent designs are under development for some of the indications.

<u>DES in peripheral arteries of the leg</u>

Decreasing restenosis and reintervention rates after implantation of coronary DES have led to the investigational use of DES in peripheral artery interventions. Feiring et al. [2004] were the first to demonstrate the safety and utility of coronary DES in tibial vessels and paved the way for a more widespread application of DES for treating infrapopliteal (i.e., below-the-knee) disease. Preliminary results from several clinical investigations using DES for the treatment of severe claudication and critical limb ischaemia in infrapopliteal lesions are encouraging [Commeau et al., 2006; Grant et al., 2008; Siablis et al., 2007a; Siablis et al., 2007b].

Diameter similarities between coronary and infrapopliteal arteries make the use of coronary DES for the treatment of lower extremity artery stenosis an intuitive application [Bosiers et al., 2008]. However, results from coronary DES application cannot be transferred to the peripheral setting [Schmehl and Tepe, 2008]. Drug release and drug loading to the stent surface must be adapted to the vessel size and lesion surface, in particular in the femoropopliteal and infrainguinal (i.e., below-the-groin) vasculature. The superficial femoral artery seems to exhibit different response characteristics to stenting and balloon angioplasty compared with coronary vessels [Dubé et al., 2007]. Furthermore, the coating process must be adjusted in case a self-expandable stent design is used. Moreover, the risk of stent fractures increases as longer lesions are stented [Scheinert et al., 2005]. At present, the longest peripheral stent has

been implanted in Germany using a 250 mm BMS for the treatment of superficial femoral and popliteal artery disease [NovoStent, 2008].
Apart from a single CE-marked DES for infrapopliteal lesions and a second one for femoropopliteal lesions (see Section 3.1); the use of DES in other leg arteries is investigational. For lesions in the superficial femoral artery, the added benefit of DES to the current generation of self-expandable BMS is questionable [Duda et al., 2006]. Although favourable DES results have recently become available with the Zilver® PTX® [Dake et al., 2011], the high price of DES is a major drawback for this technology to become the golden standard for peripheral endovascular therapy in *de novo* femoropopliteal lesions [Bosiers et al., 2010]. Nevertheless, new clinical investigations have been initiated and the results of these ongoing studies are eagerly anticipated. Ultimately, more randomised controlled trials comparing DES with BMS implantation need to be performed to determine DES superiority for the treatment of peripheral vascular disease [Bosiers et al., 2008].

DES in extracranial and intracranial arteries
DES have also been applied for the treatment of stenosis in extracranial vasculature [Gupta et al., 2006; Ko et al., 2004; Lin et al., 2008; Ma et al., 2006; Nussbaumer-Ochsner et al., 2006] and intracranial vasculature [Abou-Chebl et al., 2005; Gupta et al., 2006; Qureshi et al., 2006; Steinfort et al., 2007] but is investigational at the present. The long-term neurovascular experience with DES has yet to be published, as the field is still in its relative infancy and the safety and efficacy of neurovascular DES cannot be fully evaluated until long-term data are available. Although the DES data do not (yet) support making any changes in clinical practice, data from randomised clinical investigations using BMS warrant continued investigations [Ederle et al., 2009]. An appropriate level of caution should be taken prior to the use of DES in extracranial and intracranial arteries.

DES in renal arteries
DES use for the treatment of renal artery disease is also investigational [Granillo et al., 2005; Kakkar et al., 2006; Zähringer et al., 2007; Zeller et al., 2006; Zeller et al., 2007]. In general, DES in renal interventions provides no added benefit to the current generation of balloon-expandable BMS, except in patients with solitary functional kidneys, where treatment failure has more compelling implications [Bosiers et al., 2008] or in patients with small renal arteries (≤ 5 mm), where outcomes are less favourable [Zeller et al., 2006].

DES in coronary bypass grafts
DES use is investigational for the treatment of lesions in coronary bypass grafts, such as saphenous vein grafts [Bansal et al., 2008; Chu et al., 2006; Ge et al., 2005; Hoye et al., 2004; Latib et al., 2010; Lee et al., 2005; van Twisk et al., 2008; Vermeersch et al., 2006] and internal mammary artery grafts [Buch et al., 2006; Zavalloni et al., 2007]. Most available data on DES are on anastomotic disease. In this case, where the use of stents is imperative, there is no evidence of advantages gained by the use of DES over BMS in terms of new revascularisations. Some unanswered questions on DES use in this setting still remain. For this reason, new randomised clinical investigations are required to definitely give a reliable answer on DES efficacy in this subset of lesions [Presbitero et al., 2008]. Recent meta-analyses [Brilakis et al., 2010; Joyal et al., 2010; Sanchez-Recalde et al., 2010] on the use of DES in saphenous vein grafts concluded that data from large, prospective, randomised, controlled studies are needed to address safety and effectiveness. DES implantation in saphenous vein grafts appears to be safe and although not yet definitely proven,

likely to reduce angiographic stenosis and the need for repeat target lesion revascularisation [Brilakis et al., 2010].

3.3 Preclinical evaluation of DES

The biocompatibility of DES has to be demonstrated as part of the conformity assessment procedure and market approval procedure, respectively [EMA, 2008; European Commission, 2008; FDA, 2008]. Such tests typically include findings of cytotoxicity, sensitisation, acute toxicity, genotoxicity (mutagenicity) and haemocompatibility and, depending on the product, chronic toxicity and carcinogenicity. For the medicinal substance, additional data of the chemistry, pharmacology, pharmacokinetics and toxicology of the drug are required for demonstrating drug safety systemically and locally in the arterial wall [EMA, 2008; European Commission, 2008; FDA, 2008]. An ideal animal model for DES evaluation remains uncertain, although several excellent models have emerged. In the evaluation of the biocompatibility tests, experience suggests that porcine coronary arteries and rabbit iliac arteries are suitable in that their size, access and injury response are similar to human vessels [EMA, 2008; European Commission, 2008; Schwartz et al., 2002; Schwartz et al., 2004; Schwartz et al., 2008]. Animal models have predictive value as the sequence of biological events associated with arterial repair is remarkably similar [Virmani et al., 2003]. However, juvenile healthy animal arteries differ from aged human atherosclerotic arteries and rates of arterial healing differ among animal species [Finn et al., 2007]. The true safety and efficacy of DES can only be proven in humans and should be evaluated clinically.

3.4 Clinical evaluation of safety and effectiveness of off-label use of DES

Along with a plethora of randomised controlled trials evaluating the safety and efficacy of DES (e.g., Garg and Serruys [2010]), many observational studies reflecting real-world use of DES have been undertaken to evaluate the safety and effectiveness of DES in 'all-comers' patient populations. Clinical outcomes of several (comparative) observational studies and randomised trials with 'all-comers' design are summarised below. An extensive overview of the data from these studies included in this evaluation is given in Appendix III. Clinical outcomes of observational studies are individual end points reflecting safety, i.e., death (Table 3), myocardial infarction (Table 3), stent thrombosis (Table 4), and effectiveness, i.e., reduced need for target vessel revascularisation (Table 5). Clinical outcomes of observational studies/randomised trials comparing the new generation DES with first-generation DES (i.e., sirolimus-eluting or paclitaxel-eluting stents) and directly comparing two new-generation DES are shown for similar safety end points (Table 6-7) and effectiveness end point (Table 8).

Off-label use of DES versus on-label use of DES

Observational studies included patients treated with sirolimus-, paclitaxel-, everolimus- or zotarolimus-eluting stents with a follow-up period ranging from one year up to nearly three years [Ahmed et al., 2008; Beohar et al., 2007; Bezerra et al., 2010; Brodie et al., 2008; Flores et al., 2008; Jeremias et al., 2008; Lasala et al., 2009a; Lasala et al., 2009b; Latib et al., 2009; Lotan et al., 2009; Meredith et al., 2011; Qasim et al., 2007; Win et al., 2007].
Compared with patients treated with DES for on-label indications, a 1.29-fold increased risk of death [Brodie et al., 2008], a 1.37-fold to 2.20-fold increased risk of myocardial infarction [Brodie et al., 2008; Win et al., 2007], a 2.29-fold to 3.17-fold increased risk of stent thrombosis [Beohar et al., 2007; Bezerra et al., 2010; Win et al., 2007] and a 1.49-fold to 1.87-fold increased risk of the

need for target vessel revascularisation [Beohar et al., 2007; Brodie et al., 2008] was observed for those receiving DES for off-label indications. In some studies the numerically higher hazard ratio or odds ratio of death [Beohar et al., 2007; Bezerra et al., 2010; Flores et al., 2008; Win et al., 2007], myocardial infarction [Beohar et al., 2007; Bezerra et al., 2010; Flores et al., 2008], stent thrombosis [Beohar et al., 2007; Brodie et al., 2008] and target vessel revascularisation [Flores et al., 2008] or the numerically lower hazard ratio of myocardial infarction [Beohar et al., 2007] and odds ratio of target vessel revascularisation [Bezerra et al., 2010] were not statistically significant.[1]
Beohar et al. [2007] compared on-label use (the 'standard' group with lesions characteristics described in the manufacturer's IFU) with 'off-label' use (restenotic lesion, lesion in bypass graft, long lesion length, small and large reference vessel diameter) and 'untested' use (treatment of left main coronary artery, ostial, bifurcations or totally occluded lesion). This distinction may have contributed to the higher and lower hazard ratio of myocardial infarction in 'off-label' and 'untested' situations, respectively. In other observational studies no such distinction was made.
It appears as though off-label use of DES is associated with worse safety and effectiveness profiles than on-label. However, in all these studies there were no data comparing off-label use with an alternative treatment strategy.

Off-label use of DES versus off-label use of BMS
To further address the safety and effectiveness issue with off-label use of DES, off-label use of DES has to be compared with off-label use of BMS. It should be noted that in most situations which would represent off-label use of DES, the alternative treatment would be an off-label indication for BMS as well. Currently, data comparing off-label BMS with on-label BMS are sparse.
Several observational studies compared DES with BMS with a follow-up period ranging from one year up to four years [Applegate et al., 2008a; Austin et al., 2008; Brodie et al., 2008; Carlsson et al., 2009; Gao et al., 2009; Harjai et al., 2008; Harjai et al., 2009; Ko et al., 2009; Marroquin et al., 2008; Roy et al., 2008b]. In nearly all studies the DES group included two DES (i.e., sirolimus- or paclitaxel-eluting stents), except for one study where patients were treated with either sirolimus-, paclitaxel- or zotarolimus-eluting stents [Gao et al., 2009].
Compared with off-label use of BMS, off-label use of DES was associated with a 28%-46%[2] decreased risk of death [Applegate et al., 2008a; Austin et al., 2008; Brodie et al., 2008], 29%-38% decreased risk of myocardial infarction [Brodie et al., 2008; Marroquin et al., 2008], and 33%-65% decreased risk of the need for target vessel revascularisation [Applegate et al., 2008a; Austin et al., 2008; Brodie et al., 2008; Gao et al., 2009; Harjai et al., 2008; Harjai et al., 2009; Marroquin et al., 2008]. Some observational studies showed a numerically, albeit not significantly, decreased risk of death [Carlsson et al., 2009; Gao et al., 2009; Harjai et al., 2008; Marroquin et al., 2008], a numerically, albeit not significantly, increased risk [Austin et al., 2008; Carlsson et al., 2009] or decreased risk [Gao et al., 2009] of myocardial infarction and a numerically, albeit not statistically, decreased risk [Applegate et al., 2008a; Brodie et al., 2008; Gao et al., 2009] or increased risk [Harjai et al., 2008] of stent thrombosis.
Overall, no definite conclusions can be drawn with regard to (long-term) safety end points, such as death and myocardial infarction. The effectiveness of DES

[1] The 95% confidence interval of the hazard ratio or odds ratio included 1.0.
[2] Percentage was calculated using (1-hazard ratio)×100%.

for off-label indications, as measured by the need for revascularisation, is better than that of BMS for similar indications.

Off-label use of DES versus off-label use of other DES
In one observational study, sirolimus-eluting stents were compared with paclitaxel-eluting stents for the same off-label indications [Ruperto et al., 2009]. At three years, there were no differences between the groups in terms of death, myocardial infarction, stent thrombosis and target vessel revascularisation.

Unrestricted use of DES versus unrestricted use of BMS
Unrestricted use of DES included patients treated with sirolimus-, paclitaxel-, everolimus- or zotarolimus-eluting stents with a follow-up period ranging from one to five years [Abbott et al., 2007; Alahmar et al., 2009; Applegate et al., 2008a; Applegate et al., 2009; Auer et al., 2010; Bental et al., 2010; Daemen et al., 2009; Daemen et al., 2006; Daemen et al., 2008; Harjai et al., 2009; James et al., 2009; Jensen et al., 2007; Jensen et al., 2010; Kaltoft et al., 2009; Lagerqvist et al., 2007; Lemos et al., 2004b; Marzocchi et al., 2007; Mauri et al., 2008; Nienaber et al., 2009; Ong et al., 2006; Onuma et al., 2009; Shishehbor et al., 2008; Simsek et al., 2010b; Tu et al., 2007; Williams et al., 2006; Yan et al., 2008].
Compared with unrestricted use of BMS, unrestricted use of DES was associated with a 25%-46% decreased risk of death [Applegate et al., 2008a; Bental et al., 2010; Harjai et al., 2009; Shishehbor et al., 2008]. In a Swedish registry a 1.18-fold increased risk of death has been reported for a follow-up period up to approximately 3 years [Lagerqvist et al., 2007]. However, the Swedish data were reversed with longer follow-up, i.e., DES was associated with a numerically, albeit not significantly, decreased risk of death [James et al., 2009]. For the majority of observational studies a statistically non-significant reduction or increase in mortality was observed with unrestricted use of DES compared with BMS. In a meta-analysis, including other studies besides some of the above mentioned observational studies, a significant reduction of 22% in mortality was shown [Kirtane et al., 2009].
Clinical outcomes of myocardial infarction have been inconsistent, with one observational study reporting a significant reduction of risk of 25% [Daemen et al., 2009], some studies reporting a 1.23-fold to 4.0-fold increased risk [Jensen et al., 2007; Jensen et al., 2010; Kaltoft et al., 2009] while others reported, albeit not significantly, numerically higher [Abbott et al., 2007; Auer et al., 2010; Harjai et al., 2009; Kaltoft et al., 2009; Yan et al., 2008] or lower risk [James et al., 2009; Marzocchi et al., 2007]. A meta-analysis showed that among observational studies involving 182,901 patients, a significant reduction of 13% in myocardial infarction was observed in patients receiving DES [Kirtane et al., 2009].
Compared with BMS, unrestricted use of DES was associated with 1.75-fold to 2.06-fold increased risk of stent thrombosis [Jensen et al., 2010; Kaltoft et al., 2009]. However, numerically higher [Daemen et al., 2009; Jensen et al., 2010; Kaltoft et al., 2009] and lower [Daemen et al., 2008; Jensen et al., 2007; Jensen et al., 2010; Kaltoft et al., 2009] risk of stent thrombosis, though not statistically significant, was also observed. It should be noted that the statistically significant increased risk of stent thrombosis was shown for patients treated with paclitaxel-eluting stents. When compared with BMS, unrestricted use of DES was associated with a statistically significant 2.31-fold to 10.93-fold increased risk of very late stent thrombosis (> 1 year) but with very wide confidence intervals [Jensen et al., 2007; Jensen et al., 2010]. One observational study showed a numerically higher, albeit non-significant, risk of very late stent thrombosis [Auer et al., 2010].

Finally, the need for target vessel revascularisation in observational studies was significantly reduced, except for one study showing a lower but non-significant decrease in risk for unrestricted use of DES compared with BMS [Yan et al., 2008]. Significant reduction in the range of 29% to 65% in target vessel revascularisation was observed. This range of risk decrease is in line with the significant reduction of 46% in the meta-analysis of Kirtane et al. [2009].

Comparison of new generation DES

Several studies compared the unrestricted use of new-generation DES with first-generation DES [Kedhi et al., 2010; Mahmoudi et al., 2011; Onuma et al., 2009; Park et al., 2010; Räber et al., 2011; Rasmussen et al., 2010; Smits et al., 2011; Stefanini et al., 2011; Windecker et al., 2008; Wykrzykowska et al., 2011].

At four years, there were no significant differences between the biolimus-eluting (new-generation) and sirolimus-eluting (first-generation) stent for the individual safety end points except for very late stent thrombosis. Unrestricted use of the biolimus-eluting stent was associated with 80% decreased risk of very late definite stent thrombosis. The risk of the need for target vessel revascularisation was decreased, but it did not reach statistical significance. Data suggest that the biolimus-eluting stent has an equivalent profile for other safety end points and equivalent effectiveness to sirolimus-eluting stent in an 'all-comers' patient population [Stefanini et al., 2011; Windecker et al., 2008; Wykrzykowska et al., 2011].

The everolimus-eluting stent was found to have a similar safety profile for end point death up to one year follow-up when compared with sirolimus-eluting stent [Mahmoudi et al., 2011; Onuma et al., 2009]. At three years, however, the unrestricted use of everolimus-eluting stent was associated with 38% decreased risk of myocardial infarction and 70% decreased risk of definite stent thrombosis. Moreover, the risk of the need for target vessel revascularisation decreased by 25%. It was concluded that the long-term unrestricted use of the everolimus-eluting stent is more safe and effective when compared with the sirolimus-eluting stent [Räber et al., 2011].

When compared with the paclitaxel-eluting stent, the unrestricted use of the everolimus-eluting stent was associated with 48% decreased risk of myocardial infarction and approximately 79% decreased risk of definite stent thrombosis at follow-up of one to two years [Kedhi et al., 2010; Smits et al., 2011]. Although the risk of death was decreased at short-term follow-up [Onuma et al., 2009], it increased at longer-term follow-up but did not reach statistical significance [Kedhi et al., 2010; Mahmoudi et al., 2011; Smits et al., 2011]. In terms of effectiveness, the unrestricted use of the everolimus-eluting stent was associated with approximately 60% decreased risk of the need for target vessel revascularisation at a follow-up of one to two years [Kedhi et al., 2010; Smits et al., 2011]. It was concluded that the unrestricted use of the everolimus-eluting stent has equivalent safety and effectiveness [Mahmoudi et al., 2011; Onuma et al., 2009] or is more safe and more effective [Kedhi et al., 2010; Smits et al., 2011] than the paclitaxel-eluting stent.

The first version of the zotarolimus-eluting stent (i.e., Endeavor® stent) had less favourable clinical outcomes when compared with the sirolimus-eluting stent [Rasmussen et al., 2010]. In the meantime, a new version of the zotarolimus-eluting stent (i.e., Endeavor® Resolute stent) has become available. A trial comparing the latest version zotarolimus-eluting stent with a sirolimus-eluting stent is not yet available but has been announced [Maeng et al., 2010].

Recently, the unrestricted use of the latest version zotarolimus-eluting stent was compared with the everolimus-eluting stent, also a new generation DES. The comparison showed that patient-related outcomes (i.e., all-cause mortality, any

myocardial infarction, any repeat revascularisation) and stent-related outcomes (i.e., cardiac death, myocardial infarction, target lesion revascularisation) rates were no different between groups, nor were the event rates of any major clinical events [Serruys et al., 2010; Silber et al., 2011].

Rate of DES thrombosis

For unrestricted use of DES, the annual rate of definite stent thrombosis ranged from 0.24% to 0.63% per year for up to 4 years (interval late – very late) [Applegate et al., 2008b; Daemen et al., 2007; Pinto Slottow et al., 2008; Roy et al., 2008a; Wenaweser et al., 2008]. The annual rate of definite plus probable stent thrombosis ranged from 0.5% to 0.96% per year for up to 2 years (interval late – very late) [Applegate et al., 2009; Pinto Slottow et al., 2008; Roy et al., 2008a]. A slightly lower annual rate was observed for very late definite stent thrombosis, i.e., 0.2% per year [Jensen et al., 2010]. One obvious difference between treatment strategies among patients in these studies was the duration of the anti-platelet therapy.

Stent thrombosis is not a problem limited to DES. Case reports showed that very late stent thrombosis may occur even in BMS [Ramos et al., 2007]. Recently, a literature review evaluated differences in lesion-specific outcomes with off-label use of DES versus BMS [Beohar et al., 2010]. The overall rate of stent thrombosis (as defined by protocol) was low and similar between DES and BMS in off-label lesions (i.e., lesions in left main coronary artery, saphenous vein grafts, in-stent restenosis, ostial lesions, chronic total occlusions, long lesions and calcified lesions) at 6-12 months, except for an observed high rate of thrombosis with BMS in small vessels and with DES in bifurcation lesions. The small numbers of patients with certain lesions and the lack of information on the used anti-platelet therapy did not permit definitive conclusions.

Although the frequency of occurrence is small, stent thrombosis and its prevention will remain relevant.

3.5 Regulatory safety nets

Europe as well as the USA has two kinds of regulatory safety net to mitigate risks of DES. One safety net regulates the marketing (pre- and post) of medical devices and the other regulates the practice of medicine as exercised by physicians.

3.5.1 Placing of medical devices on the market

Europe and the USA have their own regulatory system for medical devices. In Europe, a notified body issues CE mark certificates. To place their products on the European market, manufacturers need to comply with the requirements of the European medical devices directive [Council Directive 93/42/EEC, 1993]. Except for the lowest risk medical devices, a CE mark certificate issued by a notified body is required by the medical devices directive. For drug components in combination devices, medicinal product competent authorities have to be consulted.

In the USA, the regulatory system depends on market authorisation by the FDA. Manufacturers need to apply for market approval and demonstrate compliance with all provisions of FDA guidelines to place their product on the US market [FDA, 2008].

Before high-risk medical devices such as DES are placed on the market, clinical investigations with strict inclusion/exclusion criteria are conducted to demonstrate the safety and efficacy of the medical device. The intended use of the medical device placed on the market has to closely match the inclusion criteria. For the clinical evaluation of coronary stents, special guidelines exist

[EMA, 2008; European Commission, 2008]. In Europe, DES should be clinically evaluated for a minimum of twelve months. Long-term follow-up of patients included in the clinical investigation should be performed and post-market clinical follow-up shall be considered and conducted unless duly justified. In the USA,
12-month primary end point data are required with a substantial proportion of patients having 2-year data at the time of marketing application submission [FDA, 2008]. Moreover, DES study length should be viewed in terms of the entire follow-up, which should extend through a 5-year clinical follow-up.
Risk management is obligatory in both Europe and the USA. The harmonised standard EN ISO 14971 describes a risk management process for medical devices [EN ISO 14971, 2007]. This standard requires that manufacturers also address risks related to reasonably foreseeable misuse of their device. Although it is debatable whether off-label use is misuse, this indicates that off-label use should be addressed in the risk analysis. Manufacturers are also obliged to institute and keep up to date a systematic procedure (post-market surveillance) to review experience gained from devices in the postproduction phase and to implement appropriate means to apply any necessary corrective actions, taking into account the nature and risks in relation to the product [Council Directive 93/42/EEC, 1993]. This system should yield data on the use of their devices. When an incident occurs, the manufacturer is required to notify the competent authority in their country [Council Directive 93/42/EEC, 1993; European Commission, 2009].

3.5.2 Practice of medicine

In European legislation, clinical practice is regulated at the national level. Dutch health care facilities (hospitals, nursing homes, private clinics, etc.) need to act in accordance with the law on quality of care aimed at the provision of good quality of care [Kwaliteitswet zorginstellingen, 1996]. This law provides a framework with broad requirements. It allows institutes to establish a system that fits their own situation. Health care facilities are primarily responsible for the quality of care they provide. The Dutch Health Care Inspectorate (IGZ) supervises compliance with this law. Since the primary responsibility for the provision of responsible care lies with the institute itself, the focus of supervision is on the way institutes monitor, control and improve their own quality. The government remains responsible for the quality of care in the Netherlands.
Individual active professionals are not covered by the law on quality of care. The quality of their work is ensured by the act on professions in individual health care [Wet op de beroepen in de individuele gezondheidszorg, 1993]. This Act aims at quality of practice in individual care provision (directly aimed at one person) and monitors and protects patients against incompetent and careless acts by professionals. It contains law provisions on matters such as title protection for a limited number of professions. Such a professional must meet certain legal requirements. The main requirements relate to their training. With the use of a protected title, public and insurers can check whether they are dealing with experts. Professionals with protected titles are registered by the government and they have to apply for registration. This is only granted if the applicant meets the requirements. Training is the most important requirement. Registered professionals, but also third parties, can request information from the registry. Only registered persons may perform professional acts and they fall under the disciplinary law (for improving and monitoring the quality of the profession).
Specifically for performing PCI, Dutch hospitals need an authorisation. PCI falls under a law for special medical care [Wet op bijzondere medische verrichtingen,

1997]. In April 2008, five hospitals were authorised to carry out PCI. In addition, thirteen hospitals applied for authorisation. Recently, the Dutch minister of Health Welfare and Sports worded the intention to eliminate this authorisation procedure in a letter [VWS, 2009]. New PCI centres should meet the quality requirements of the Dutch Society of Cardiology (NVVC). The NVVC states inter alia that hospitals should have two catheterisation rooms and four intervention cardiologists, 24-hour availability should be guaranteed and at least 600 PCI per year should be performed. According to the minister, it is possible in the near future to meet the necessary preconditions: the criteria of the NVVC are feasible to inspect upon and every PCI centre should participate in the Dutch Coronary Interventions Data Registry, which is under development.
In the USA the FDA Modernization Act explicitly articulates: 'Nothing in this Act limits or interferes with the authority of a physician to prescribe or administer any legally marketed device to treat any disease or condition if done within a legitimate health care practitioner-patient relationship. However, FDA retains its current authority to restrict the sale, distribution, or labelling of devices and to prohibit the promotion of unapproved uses' [FDA, 1997]. This means that off-label use of medical devices approved for other indications is allowed under the professional responsibility of the physician.
Whereas there is a demarcation within the FDA Modernization Act 'FDA retains its current authority to restrict the sale, distribution, or labelling of devices and to prohibit the promotion of unapproved uses' [FDA, 1997], the FDA also recognises the value of having new indications and intended uses for products approved or cleared by FDA. The FDA therefore encourages sponsors of medical products to seek such approvals or clearances. Accordingly, the public health may be advanced by the availability of medical journal articles and medical or scientific reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading. In recognition of the public health value to healthcare professionals of receiving truthful and non-misleading scientific and medical information, the FDA provided recommendations for the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of medical devices and drugs [FDA, 2009].

3.6 Clinical practice guidelines

Clinical practice guidelines help physicians to weigh the benefits and risks of a particular diagnostic and therapeutic procedure. Guidelines for interventional cardiologists use a grading system based on levels of evidence and classes of recommendations (Box 4).
Guidelines reflect a consensus of expert opinion. Consensus is achieved for all recommendations on the basis of evidence. The class of recommendation (I, II, IIa, IIb or III) indicates the strength of the recommendation of a particular treatment option based on an objective judgment about the relative merits of the data. In simple terms, class I recommendations are the 'do's', class II recommendations are the 'maybes', and class III recommendations are the 'don'ts'. The level of evidence (A, B or C) includes a description of the existence and types of studies available supporting the recommendation and expert consensus. The strongest weight of evidence (A) is assigned if there are multiple randomised trials with large numbers of patients. An intermediate weight (B) is assigned if there is a limited number of patients, careful analyses of non-randomised trials or observational studies. The lowest rank of evidence (C) is assigned when expert consensus is the primary basis for the recommendation. The assignment of a C level of evidence to a class I recommendation should not be interpreted to mean that this is a 'weak' recommendation. This may simply

reflect the ethical or logistical difficulty of ever performing a randomised trial to test the treatment or procedure in question [Gibbons et al., 2003]. Basically, guidelines can be classified into the following categories:

- Interventional procedure-based guidelines;
- Disease-based guidelines and;
- Diagnostic procedure-based guidelines.

Clinical practice guidelines were examined closely for recommendations concerning DES use.

Box 4. Pre-defines scales for classes of recommendations and levels of evidence [Silber et al., 2005; Smits et al., 2006; Wijns et al., 2010]

Classes of recommendations

Class I – Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective;
Class II – Conflicting evidence and/or divergence of opinion about usefulness/efficacy of the treatment or procedure;
Class IIa – Weight of evidence/opinion is in favour of usefulness/efficacy;
Class IIb – Usefulness/efficacy is less well established by evidence/opinion;
Class III – Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful.

Levels of evidence

Level A – Data derived from multiple randomised trials or meta-analysis;
Level B – Data derived from a single randomised clinical trial or large non-randomised studies;
Level C – Consensus of opinion of the experts and/or small studies, retrospective studies, or registries.

3.6.1 European guidelines for coronary artery diseases

The ESC publishes annual reports, analyses and guidelines regarding interventional cardiology. In 2005, the first ESC guidelines for PCI were issued covering many indications [Silber et al., 2005]. The ESC also issued several disease-based guidelines that overlap to a considerable extent with the current ESC guidelines for PCI [Bassand et al., 2007; Fox et al., 2006; Ryden et al., 2007; Van de Werf et al., 2008]. In 2010, the ESC and the European Association for Cardio-Thoracic Surgery (EATCS) issued guidelines on myocardial revascularisation [Wijns et al., 2010].
The purpose of these guidelines is to give practically-oriented recommendations on when to perform PCI using currently available published data derived from randomised and non-randomised clinical studies. An overview of PCI recommendations based on ESC guidelines is given in Table 9 (Appendix IV). According to ESC guidelines, 'PCI can be considered a valuable initial mode of revascularisation in all patients with objective large ischaemia in the presence of almost every lesion subset, with only one exception: chronic total occlusion that cannot be crossed. […] The addition of stents and newer adjunctive medications improved the outcome of PCI' [Silber et al., 2005]. Thus, PCI is an umbrella term of various catheter-based interventions, e.g., (direct) stenting, balloon angioplasty, primary PCI or rescue PCI.
It should be noted that the term off-label has been introduced after the FDA Advisory Panel meeting in the ESC/EACTS guidelines [Wijns et al., 2010] as well as the US guidelines written by the American College of Cardiology (ACC), the American Heart Association (AHA) and the Society for Cardiovascular

Angiography and Interventions (SCAI) [King et al., 2008]. Also, class III recommendation is not defined in the ESC guidelines for PCI, whereas a class III recommendation is included in more recent ESC guidelines (e.g., Bassand et al. [2007], Wijns et al. [2010]), as well as current ACC/AHA/SCAI guidelines for PCI [King et al., 2008]. DES indications requiring further evidence-based evaluation are given in Table 10.

Table 10. Class of recommendation and level of evidence for DES indications [Silber et al., 2005]

Indications	Class	Level
Small vessels	IIa	C
Chronic total occlusion	IIa	C
Bifurcation/ostial lesions	IIa	C
Bypass stenoses	IIa	C
Insulin-dependent diabetes mellitus	IIa	C
Multi-vessel disease	IIa	C
Unprotected left main stenoses	IIa	C
In-stent restenoses	IIa	C

3.6.2 Dutch guidelines for coronary artery diseases

The Dutch Society of Cardiology (NVVC) has issued:

- Dutch guidelines for PCI [NVVC, 2005], based on ESC guidelines [Silber et al., 2005] and;
- Guidelines for DES written by the Dutch Working Group on Interventional Cardiology [Smits et al., 2006].

The first guidelines are essentially a Dutch translation from previous ESC guidelines. In addition, the NVVC website listed current ESC guidelines (see Section 3.6.1). However, the NVVC website is inconclusive on superseded guidelines. In the Dutch guidelines for DES, classes of recommendations (i.e., denoted in guidelines as usefulness or efficacy) and levels of evidence are given for indications (Table 11). Noteworthy is that recommendations for four different types of DES have been included in the guidelines, which are lacking in the ESC guidelines. In the Dutch guidelines the term off-label indication is also not used. However, a number of indications in the guidelines are off-label for a certain number of currently available DES. Furthermore, the guidelines for DES had higher classes of recommendations and levels of evidence compared to the ESC guidelines.

3.6.3 Guidelines and dual anti-platelet therapy

Dual anti-platelet therapy (combined prescription of aspirin and thienopyridines, i.e., clopidogrel or pasugrel) is warranted to guarantee optimal stent performance and patient clinical well-being [Waksman, 2006]. The optimal duration of dual anti-platelet therapy is, however, unknown. Multiple studies indicate increased rates of stent thrombosis, myocardial infarction or mortality associated with premature discontinuation of dual anti-platelet therapy [Eisenberg et al., 2009; Iakovou et al., 2005; Jeremias et al., 2004; Park et al., 2006; Pfisterer et al., 2006; Spertus et al., 2006].
European guidelines for PCI recommend 6-12 months anti-platelet therapy after DES implantation [Silber et al., 2005]. Dutch guidelines recommend at least 9-12 months [Smits et al., 2006] (Table 12). US guidelines recommend anti-platelet therapy for at least 12 months after DES implantation if patients are not at high risk of bleeding [King et al., 2008]. According to the FDA guideline for

DES, eventual product labelling should include both the prescribed anti-platelet therapy and patient compliance with that therapy as experienced in the clinical trials and should clearly specify the risks of premature anti-platelet medication discontinuation [FDA, 2008]. Some investigators suggest that the exact duration of treatment should be determined on an individual patient basis after careful consideration of the competing risks of stent thrombosis and bleeding [Love et al., 2007], while others suggest that the therapy should be continued indefinitely until more information is available [Benezet-Mazuecos et al., 2007].

Table 11. Class of recommendation and level of evidence for DES indications [Smits et al., 2006]

	SES		PES		ZES		TES	
Indications for use	Class	Level	Class	Level	Class	Level	Class	Level
Non-complex lesions[†]	I	A	I	A	IIa	B	IIb	B
Moderate complex lesions[‡]	I	A	I	A	-	-	-	-
Small vessels[¶]	I	B	I	B	-	-	-	-
Long lesions[§]	I	B	I	B	-	-	-	-
STEMI lesions	IIa	B	IIa	B	-	-	-	-
Diabetes mellitus patients	I	A	I	A	IIa	C	-	-
In-stent restenosis lesions	I	A	I	B	-	-	-	-
Chronic total occlusion lesions	I	A	I	B	-	-	-	-
Bifurcation/ostial lesions	I	C	I	C	-	-	-	-
Unprotected left main lesions	I	B	I	B	-	-	-	-
Multi-vessel disease	I	B	I	C	-	-	-	-

Abbreviations: DES – drug-eluting stent, PES – paclitaxel-eluting stent, SES – sirolimus-eluting stent, STEMI – ST-segment elevation myocardial infarction, TES – tacrolimus-eluting stent, ZES – zotarolimus-eluting stent

[†] Non-ostial, non-calcified, non-thrombus containing lesions in native vessels (lesion length < 30 mm with reference vessel diameter of 2.5-3.5 mm) in patients with stable or unstable angina.

[‡] *De novo* lesions in native vessels (lesion length 18-40 mm with reference vessel diameter of 2.5-3.5 mm) in patients with stable or unstable angina.

[¶] Reference vessel diameter 2.25-3.0 mm.

[§] Length of lesion > 40 mm.

Table 12. Adjunctive medications with DES [Smits et al., 2006]

Indications	Class	Level
Acetylsalicylic acid	I	C
Clopidogrel for at least 9-12 months	I	C
Heparin	I	C
Bivalrudine	IIb	C
Fractionated heparin	IIb	C

Factors contributing to premature cessation of anti-platelet therapy include physician/dentist instructions to patients to discontinue therapy before procedures and inadequate patient education and understanding about the importance of continuing therapy [Bosiers et al., 2008; Grines et al., 2007]. These factors should be considered before placing a DES [Grines et al., 2007; Love et al., 2007; Zijlstra, 2007]. However, acute situations do not usually permit such an evaluation [Zijlstra, 2007].

3.6.4 European guidelines for peripheral artery disease

The Cardiovascular and Interventional Radiological Society of Europe (CIRSE) has issued quality assurance/improvement guidelines for clinical practice and

standards based on published evidence for interventional radiologists. These quality assurance guidelines or standards may have been adopted from previous guidelines issued by the US Society of Interventional Radiology (SIR); they may be new guidelines produced by CIRSE or they may be new documents produced as joint ventures between CIRSE and SIR. Relevant guidelines are addressing:

- Endovascular treatment of occlusive lesions of the sub-clavian and innominate arteries [CIRSE, a];
- Performance of carotid stenting [CIRSE, b];
- Endovascular treatment of iliac artery occlusive disease [CIRSE, c];
- Stenting of infrainguinal arterial disease [CIRSE, d], and;
- Endovascular management of aortic occlusive disease [CIRSE, e].

In European guidelines for the treatment of peripheral artery disease, DES implantation has not yet been addressed. The ESC has scheduled guidelines for peripheral artery disease to be issued in 2011.

3.6.5 Remaining uncertainties

It often happens that physicians have to deal with complex morbidities for which there is no clear treatment guideline with level I evidence to support it. This means that a physician might end up opting for off-label use based on lower levels of evidence and/or expert medical opinion.

4 Discussion, conclusions and recommendations

4.1 DES inventory

The inventory revealed a marked difference between the number of CE-marked DES (n=61) compared with FDA-approved DES (n=14). The indications for use of CE-marked DES were often not mentioned on the manufacturer's web site. Nevertheless, the inventory revealed more expanded indications for CE-marked coronary DES compared with FDA-approved DES. The indications for use of 14 CE-marked DES included broadened vessel and lesion characteristics as well as patient characteristics after the initial CE mark was obtained. Recently, new DES specifically designed for bifurcations and peripheral vasculature have become available and several more are in various stages of development. In the USA, the indications for use of five approved DES were expanded at a later date for vessel and lesion characteristics. DES for bifurcations and peripheral vasculature are not yet approved in the USA.
It is unclear why this difference exists between the numbers of available DES in the market in Europe and the USA. The data on medical devices in the USA were extracted from a database maintained by the FDA's Center for Medical Devices and Radiological Health. A similar European database, known as Eudamed, is not yet available but will be operational soon [European Commission, 2010].
An important limitation of the web search with regard to our purposes was the fact that manufacturer's web sites contain limited information on indications for use. Promotional material (e.g., brochures) or press releases announcing the certification of the notified body for affixing the CE mark, hardly ever mentioned indications as can be found in the IFU, which was not always published on the manufacturer's web site. The FDA database also contained information on approved indications for use, as stated in the IFU.
Although we are fairly confident that the identified CE-marked DES from 29 manufacturers represent the market in Europe, the actual number of DES with CE mark and on the European market might differ slightly, since we had to rely on web searches.

4.2 Frequency of occurrence of off-label use of DES

Off-label use of DES worldwide
Single and multi-centre studies in Europe, Asia and the USA showed that the frequency of coronary DES use in patients with off-label indications ranges between approximately 47% and 81%. Apparently, off-label use of DES is common in clinical practice in various countries across the world. Several factors may partly account for the considerable range of reported off-label use of DES worldwide. First, the definition of off-label use was not consistent among the studies (e.g., differences in lesion and vessel characteristics). Second, off-label use of DES is a moving target in time. For some DES the indications for use expanded within two to three years after the initial market introduction and more DES are used for more on-label indications. Another factor is that data were obtained from single-centre registries as well as national registries. For some national registries participation was voluntary and not all PCI centres within a specific country were involved. Fourth, data on off-label use were collected from either one specific DES or more DES (e.g., sirolimus-eluting stent and paclitaxel-eluting stent). Fifth, the time window for collecting data on off-label use varied. In the Netherlands, the first registry on the use of DES started in April 2002 immediately after the availability of the CYPHER™ stent, whereas in Germany patients were enrolled in the DES.DE registry from October 2005 to

October 2006. Between April 2002 and October 2006, the two major DES platforms (CYPHER™ and TAXUS™) expanded their indications. Sixth, cost aspects, as DES are more expensive than BMS. Seventh, more dedicated DES are entering the market. Thus, it can be expected that the extent of off-label use of DES will change. There may be other factors as well.

Off-label use of DES in the Netherlands

No publications were found on the frequency of occurrence of off-label use of DES in the Netherlands at a national level. Although most PCI centres have databases, data from only one PCI centre (RESEARCH registry, Erasmus Medical Center) have been reported indicating 68% off-label use of coronary DES immediately upon market release of the CYPHER™ stent in 2002. Still, the RESEARCH data represent off-label use of first-generation DES from a single high-volume pioneering PCI centre. It is debatable whether the data are a reasonable reflection of contemporary clinical practice in the Netherlands. In PCI centres of the Rotterdam region (Erasmus Medical Centre and Maasstad Hospital) DES are used as a default strategy whereas in other high-volume Dutch PCI centres DES and BMS use is mixed. No data were identified on the percentage of off-label use with DES or BMS in these centres. Recently, several new, low-volume PCI centres have emerged which may be expected to include a lower percentage of off-label use of DES. Low-volume PCI centres are likely to perform less complex PCIs.

Registration of DES use in the Netherlands

As for now, there is no national registry with publicly available information on DES use in all Dutch PCI centres. The Dutch minister of Health Welfare and Sports is confident that an operational Coronary Interventions Data Registry will appear soon [VWS, 2009]. A national registry would make the treatment results per centre and per individual therapist more transparent. It would also enable these results to be assessed against accepted quality standards. Making the registration system more public and more transparent would bring benefits in terms of the quality of the procedures involved and their safety for patients [Health Council of the Netherlands, 2007].

Limitations of search strategy

There are some limitations to our literature search strategy. First, we used general search terms such as unrestricted use and off-label use. Terms for specific indications (e.g., bifurcations, diabetes, ST-segment elevation myocardial infarction, etc.) were not included as this would increase the number of publications to be reviewed to a level far outside the possibilities of the budget of this study. Publications on such specific patients and lesions subgroups, which resulted from our search, were also not selected for our analysis of clinical safety and effectiveness. Second, (brand) names of DES were not included in the search strategy. We cannot exclude that some publications were overseen, but perusing reference lists of publications should limit this problem. For this purpose an entry into the vast amount of available publications was obtained by using general search terms. In addition, we asked for input from recognised experts in the field. In conclusion, we are therefore confident that there are no major gaps in the analysis.

4.3 Safety and effectiveness of off-label use of DES

Current data show an overall poorer outcome with off-label use of DES compared with on-label use. Although data for BMS are sparse, it has been observed that the incidence of late and very late stent thrombosis was

significantly increased among patients treated for an off-label indication compared with an on-label indication [Doyle et al., 2007; Hoffmann et al., 2009]. These differences in outcome are likely related to patient or specific coronary lesion characteristics or co-morbidities, which predispose an individual to adverse outcomes regardless the type of stent used, i.e., DES or BMS.
When comparing off-label use of DES with BMS, no conclusions can be drawn with regard to (long-term) safety end points, such as death and myocardial infarction. The effectiveness of DES for off-label indications, as measured by the need for revascularisation, shows a clear advantage over BMS for similar indications.
It has to be noted that our results do not include randomised trials in patient groups with specific off-label indications. In some of these dedicated studies more definite conclusions may be possible. For example, the HORIZONS-AMI trial showed a sustained benefit of paclitaxel-eluting stents in terms of safety and efficacy for patients with one of the off-label indications (i.e., ST-segment elevation myocardial infarction) compared with BMS after a follow-up of three years [Stone et al., 2008; Stone et al., 2011]. It is unlikely that more randomised trials comparing new-generation DES with BMS for particular off-label indications will be conducted, as this may be perceived as unethical.
For unrestricted use, there are no conclusive data from individual observational studies with regard to safety aspects of DES versus BMS. However, based on a meta-analysis of observational studies by renowned investigators, DES use was associated with reduced death and myocardial infarction [Kirtane et al., 2009]. In randomised controlled trials, no significant differences were observed in the long-term rates of either death or myocardial infarction after DES or BMS use for both off-label and on-label indications [Kirtane et al., 2009]. In addition, both randomised controlled trials and observational studies demonstrated marked and comparable reductions in repeat revascularisation with DES compared with BMS. Kirtane et al. concluded that unrestricted use of DES compared with BMS did not appear to be associated with adverse safety outcomes and was more effective.
Not all DES are equal in safety and effectiveness. Unrestricted use of some new generation DES has been shown to be more safe and effective when compared with first-generation DES. More very large randomised controlled trials, real-world registries, and/or meta-analyses will be required to prove superiority of new generation DES. New generation DES (i.e., biolimus-eluting, everolimus-eluting stents) have an equivalent safety profile when compared with sirolimus-eluting stents and have equivalent effectiveness to sirolimus-eluting stents. However, the first zotarolimus-eluting stent (i.e., Endeavor® stent) showed less favourable outcomes when compared with the sirolimus-eluting stent. This might be the result of differences in biological activity of zotarolimus compared with sirolimus. Another potential reason could be more rapid elution kinetics of zotarolimus from the phosphorylcholine polymer. Compared with paclitaxel-eluting stents, the everolimus-eluting stent has favourable clinical outcomes. It has been concluded that paclitaxel-eluting stents should no longer be used in everyday clinical practice [Kedhi et al., 2010].
It is well recognised that randomised clinical trials are the gold standard to evaluate safety and efficacy of therapeutic procedures. However, they may not reflect the ‘real world’ of clinical practice. As a result, clinically relevant groups of patients are underrepresented and the generalisability of the results of randomised trials to a broader population can be questioned. Trials with ‘real world’ or ‘all-comers’ design are emerging in cardiology to improve this generalisability. Although in an ‘all-comers’ trial it is not to be expected that each and every consecutive patient will be enrolled [de Boer et al., 2011].

It is accepted now that DES use does result in an increased risk associated with very late stent thrombosis compared with BMS [Girod et al., 2008]. However, by markedly reducing restenosis-related adverse events that would have occurred with BMS, DES may directly reduce the subsequent occurrence of death and myocardial infarction, offsetting the incremental stent thrombosis risk as was reported for on-label indications of paclitaxel-eluting stents [Stone et al., 2007]. Data of observational studies with an 'all-comers' design provide an important link between randomised controlled trials and the real world, also assessing the huge number of patients who are not eligible in randomised controlled trials because of strict selection criteria. Although in an 'all-comers' trial it is not expected that each and every consecutive patient will be enrolled, they provide valuable additional information during post market surveillance of DES documenting real-world application and outcomes in everyday clinical practice. Evidence from such real-world settings is vital, and will not only document the current value of DES, but may also provide a solid foundation to guide further developments and clinical decision-making along the path on which DES will proceed.
The biocompatibility of DES has to be demonstrated as part of the conformity assessment procedure/regulatory approval procedure. Since there is no animal model for human vascular disease, preclinical safety and efficacy should be confirmed clinically. For this reason, a logical approach could be to allow the off-label use of DES only for those products that have documented long-term clinical follow-up data for on-label indications. Off-label use of coronary DES, as well as BMS, may push the devices beyond their design limits and thus potentially lead to increased risks. The FDA has recommended that DES labelling should include a warning that patient outcomes may not be as favourable as the results observed in the clinical investigations when DES are used off-label [FDA, 2007]. In our opinion such an approach should also be applicable to BMS.
The controversy surrounding DES shows the importance of studying new technologies in various patient populations. When using coronary DES off-label in peripheral arteries, it should be realised that results from coronary DES application cannot be transferred to other settings.

4.4 Rationale for off-label use of DES

Safety concerns changed the research focus to larger clinical investigations with 'all-comers' design and longer clinical follow-up. There is definitely a need for more 'all-comers' studies. On-label indications of DES are predominantly limited to relatively simple situations in fairly stable patients. The limitation originates from the fact that DES manufacturers generally design pivotal clinical investigations with limited indications for use in order to maximise the chance of demonstrating safety and performance of DES, while minimising the risk of death or procedural complications. This way, the likelihood of approval is improved. It has been argued that the economic interests of the manufacturer heavily, if not entirely, influence the extent of a device's on-label indications for use. DES may never be labelled for some indications because the size of the market is not large enough to provide an incentive to invest in clinical investigations mandated by the regulatory process [Price and Teirstein, 2008]. In regular clinical practice, however, patients with multiple lesions, lesions at bifurcations or thrombotic lesions, and in conditions such as ST-segment elevation myocardial infarction, in-stent restenosis and chronic total occlusions also have to be treated. The promising results with DES in on-label indications have led clinicians to use DES also in more complex, off-label situations, culminating in unrestricted use of DES in the 'real world'. It is considered a very important and in some cases even the only treatment option available for the

vast majority of patients with coronary lesions necessitating medical interventions. The alternative to off-label use of DES is usually off-label BMS. Manufacturers could opt for amending the indications for use in the IFU. However, specific claims regarding the expansion of indications must be backed up by specific clinical data [Russell et al., 2006]. Nearly all manufacturers placing DES on the market with expanded indications are leaders in the field of cardiovascular medical devices industry. These leading companies have the resources to conduct and finance lengthy and costly clinical investigations and have the stamina to complete the conformity assessment procedure/regulatory approval procedure. Competitors may have fewer resources or may deliberately refrain from expansion of indications.

Practice of medicine

Generally, DES indications for use in Europe are broader than in the USA (Table 1, 2). Therefore, a certain device may be used for a particular indication off-label in the USA, while the same device is used on-label in Europe for the same indication. Obviously, off-label use decreases with an increase in on-label indications.

Besides data on unrestricted use of DES based on three major single-centre registries in the Netherlands, it is remarkable that we could not find publications on the frequency of occurrence of off-label use of DES at a national level in the Netherlands, whereas in the USA many publications on the subject appear. This could be related to a lower frequency of occurrence of off-label use in the Netherlands. The lack of publications in the Netherlands may also be related to the regulatory situation. Dutch regulations do not contain explicit rules about off-label use. In the USA, off-label use of medical devices is regarded an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine [Ansel and Jaff, 2008]. Once a device has been approved or cleared by the FDA, a healthcare professional may lawfully use that product to treat any condition he/she determines is medically appropriate. Dutch physicians are obliged by law to explain risks and benefits of the treatment to their patient [Wet op de geneeskundige behandelingsovereenkomst, 1994]. Off-label use implies that clinical investigations with the device were not designed to cover the off-label indication. The implications related to this lack of clinical evidence in terms of risk and benefit should be explained to the patient. It could even be argued that the patient (or a relative) should be asked to sign an informed consent before performing the procedure. Furthermore, we believe physicians should realise that it is important to share the results of new uses of DES with colleagues and manufacturers, e.g., by publishing in scientific journals. The proposed national Coronary Interventions Data Registry (see Section 4.2) could also be useful for this purpose.

Clinical practice guidelines

For optimal clinical practice, it is of utmost importance that the latest information is publicly available. For the Dutch guidelines on the NVVC web site it was not clear whether they were superseded by current ESC guidelines. There might be a discrepancy between guidelines, which would be an undesirable situation. Moreover, stent differentiation has been included in the Dutch guidelines for DES, which is lacking in the current ESC guidelines. In addition, recommendations for DES have shifted to more class I recommendations based on higher levels of evidence (i.e., level A or B). This trend is not unexpected given the recent quantity of published scientific literature and is mirrored by the increase in number of recommendations included in ACC/AHA guidelines [Tricoci et al., 2009].

Physicians need to exercise caution when considering recommendations not supported by solid evidence. However, physicians should not discount the recommendations that are based on lesser level of evidence and expert opinion in the absence of better designed and conducted clinical investigations. There is a need for more efficient updating of the guidelines. It has been understood in clinical practice for many years that there is a lag time between recent advances in clinical trials and the guidelines. The evidence base used to create guidelines changes quickly. It has been reported that most guidelines become outdated after five years [Shekelle et al., 2001]. The ACC/AHA guidelines are periodically updated, with updates taking a mean of 4.6 to 8.2 years until publication [Tricoci et al., 2009]. As a result, many physicians apparently consider the guidelines to be (somewhat of) a historical reference and do not use them. A suggestion to improve the quality of the guidelines is to add specific and focused amendments as new data become available. Rather than to wait for the next cycle of guidelines to be required, amendments particular to a treatment or therapy should be added closer to the time data arise. According to some authors, guidelines should rather be considered a general reference than a specific indication on how to treat a specific patient [Shaneyfelt and Centor, 2009]. It would be valuable to know how physicians in the Netherlands feel about the current clinical practice guidelines.

4.5 Conclusions

- The off-label use of coronary DES has increased in frequency over time up to 47-81% worldwide, but dropped dramatically following the ESC Congress in 2006 and the consensus statements from the FDA in 2007 recommending careful consideration of DES use for off-label indications.
- Off-label use of DES in one Dutch high-volume cardiovascular centre was estimated to be 68% from April 2002 to October 2002. At a Dutch national level, no overall or metadata on the frequency of off-label use of DES could be found.
- The risk associated with off-label use is increased when compared with on-label use regardless for which type of stent, i.e., DES or BMS. This can be expected in patients with off-label indications having a higher risk profile with more complex lesions and/or co-morbidities. Patients have to be treated and the alternative to off-label use of DES is usually off-label BMS.
- Off-label use of DES is associated with decreased need for repeat revascularisation compared with off-label use of BMS.
- For unrestricted use of DES, there are no conclusive data from individual observational studies with regard to safety aspects compared with BMS for similar indications. However, in a meta-analysis by renowned investigators of observational studies and randomised clinical trials, unrestricted use of DES compared with BMS did not appear to be associated with adverse safety outcomes and was reported to be more effective.
- Some new-generation DES are more safe and effective when compared with first-generation DES.
- Treatment regimens implying off-label use of DES are important in clinical practice, offering options to treat patients with coronary lesions. In some cases, off-label use is the only treatment option available. With growing experience, off-label use may become a medically-recognised standard of care and may be important for further innovation.
- In Europe, more DES are marketed for broader indications for use compared to the USA.

- Currently, dedicated DES for more complex lesions are evaluated in clinical investigations. This may lead to decreased use of coronary DES in off-label indications, if they become available on the market.

4.6 Recommendations

- The safety and effectiveness of using DES off-label as compared with those of alternative treatments deserve continued study. Especially the safety on long-term outcome becomes more important.
- Further research is recommended to collect information on off-label use in the Netherlands by means of a survey. The survey should be aimed at interventional cardiologists and interventional radiologists. The survey should address qualitative and quantitative aspects of off-label use as well as names of manufacturers and brand names of DES actually being used in the Netherlands.
- Further research should include an inventory of indications, contraindications, warnings and precautions of CE-marked DES. Manufacturers should be requested to submit relevant information.

Acknowledgements

The authors would like to acknowledge Dr P.C. Smits (Interventional Cardiologist, Maasstad Ziekenhuis Rotterdam) for the peer review of this report on behalf of the Dutch Society of Cardiology (NVVC).

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List of abbreviations

ACC:	American College of Cardiology
AHA:	American Heart Association
BMS:	Bare metal stent(s)
CE:	Conformité Européenne
CIRSE:	Cardiovascular and Interventional Radiological Society of Europe
DES:	Drug-eluting stent(s)
EACTS:	European Association for Cardio-Thoracic Surgery
EMA:	European Medicines Agency
ESC:	European Society of Cardiology
FDA:	Food and Drug Administration
IFU:	Instructions for use
IGZ:	Inspectie voor de Gezondheidszorg (Health Care Inspectorate)
NVVC:	Nederlandse Vereniging voor Cardiologie (Dutch Society of Cardiology)
PCI:	Percutaneous coronary intervention(s)
SCAI:	Society for Cardiovascular Angiography and Interventions

Appendix I CE-marked DES

The regulatory process in Europe relies on notified bodies, which are independent commercial organizations to implement regulatory control over medical devices. Notified bodies have the ability to issue the CE (Conformité Européenne) mark. Notified bodies are designated, monitored and audited by the relevant member states via national competent authorities. A notified body has to consult one of the competent authorities of the member states or the European Medicines Agency (EMA) with regards to the quality, safety and usefulness of the medicinal substance incorporated as integral part of the device, taking into account the intended purpose of the device. Currently, 57 DES are CE-marked (including 54 DES exclusively for coronary artery disease, 2 DES for coronary as well as peripheral artery disease, and 1 DES exclusively for peripheral artery disease) and 14 DES have expanded indications for use (Table 1).

Table 1. Overview of CE-marked DES

Manufacturer	Medical device	Indications for use	CE mark	Notified body
Biolimus A9™-eluting stent				
Biosensors International (Singapore)	BioMatrix®	No information[1]	Jan 2008	0344 – Netherlands
	BioMatrix®	Small vessel[2]	Mar 2009	0344 – Netherlands
	BioMatrix Flex™	No information	Jan 2010	No information
	BioMatrix Flex™	STEMI, ACS, diabetes mellitus	May 2010	No information
	BioMatrix Flex™	Long vessel[3]	Sep 2010	No information
Devax (USA) ¶¶	AXXESS™	Coronary bifurcation lesion	Jul 2010	No information
Terumo (Japan)	Nobori™	No information[4]	Jan 2008	0482 – Germany
XTENT (USA) ‡	XTENT® Custom NX36	Single, multiple or long lesion[5]	Mar 2009	No information
	XTENT® Custom NX60	Single, multiple or long lesion[6]	Mar 2009	No information
Everolimus-eluting stent				
Abbott Vascular (USA)	XIENCE™ V†	No information[7]	Jan 2006	No information
	XIENCE™ V†	Small vessel[8]	Mar 2008	No information
	XIENCE™ V	Diabetes, complex disease including dual vessels, jailed side branches	Nov 2009	No information
	XIENCE PRIME™	No information[9]	Jun 2009	No information
	XIENCE PRIME™	Diabetes, complex disease including dual vessels, small vessels, jailed side branches	Nov 2009	No information
	XIENCE PRIME™	Severe claudication and critical limb ischaemia in infrapopliteal lesion[10]	Jan 2011	No information
	ABSORB™	No information[11]	Jan 2011	No information
Boston Scientific (USA)	PROMUS™ ††	No information[12]	Oct 2006	No information
	PROMUS™	Small vessel[13]	-	No information
	PROMUS™ Element™	No information[14a/b]	Nov 2009	0344 – Netherlands
	PROMUS™ Element™	Diabetes, STEMI	Sep 2010	No information

Table 1. Overview of CE-marked DES (continued)

Manufacturer	Medical device	Indications for use	CE mark	Notified body
Novolimus-eluting stent				
Elixir Medical (USA)	DESyne™	No information	May 2011	No information
Paclitaxel-eluting stent				
Aachen Resonance (Germany)	ARtax®	No information[15]	§	No information
Alvimedica Medical Technologies (Turkey)	Coraxel	No information[16a/b]	Dec 2009	0437 – UK
amg International (Germany)	Pico Elite	No information[17a/b]	Jan 2006	0124 – Germany
Balton (Poland)	Luc-Chopin²	No information[18]	§§	No information
	PAXEL®	No information	§§	No information
B. Braun Melsungen (Germany)	Coroflex® Please	No information[19]	§§	0123 – Germany
Biosensors International (Singapore)	Axxion™	No information[20]	Jul 2005	0344 – Netherlands
Boston Scientific (USA)	TAXUS™ Express²™	No information	Jan 2003	No information
	TAXUS™ Express²™	Large vessel[21]	Apr 2005	No information
	TAXUS™ Liberté™	No information	Sep 2005	No information
	TAXUS™ Liberté™	Restenotic lesion in BMS, total occlusion, STEMI, large vessel[22]	May 2006	No information
	TAXUS™ Liberté™ Long	Long lesion[23]	May 2007	No information
	TAXUS™ Liberté™	Diabetic patients with CAD[24]	Dec 2007	No information
	TAXUS™ Element™	Diabetic patients[25]	May 2010	No information
Cook Medical (USA)	Zilver® PTX®	Femoropopliteal artery lesion[26]	Aug 2009	0088 – UK
eucatech (Germany)	eucaTAX	No information[27a/b]	? 2007	No information
Eurocor (Germany) ‡‡	Genius TAXCOR®	No information[28]	Jul 2006	0481 – Germany
	Taxcor Plus	No information	Jan 2010	No information
Globamed (Switzerland)	Omega™	No information[29]	§	0481 – Germany
Iberhospitex (Spain)	Active®	No information[30a/b/c]	May 2008	0318 – Spain
InTek Technologies (Switzerland)	Apollo	Acute or impending occlusion in connection with a coronary operation[31]	§	0124 – Germany

Table 1. Overview of CE-marked DES (continued)

Manufacturer	Medical device	Indications for use	CE mark	Notified body
Paclitaxel-eluting stent				
Minvasys (France)	Nile Pax®	Coronary bifurcation lesion[32]	Dec 2009	0459 – France
	Nile Delta®	Coronary bifurcation lesion[33]	Dec 2009	0459 – France
	Amazonia® Pax	No information[34]	Jan 2010	0459 – France
Sahajanand Medical Technologies (India)	Infinnium®	Coronary lesion with reference vessel diameter ≥2.25 mm to ≤4.0 mm[35]	Dec 2005	0434 – Norway
Stentys (France)	Stentys™	Coronary bifurcation lesion	May 2010	No information
Vascular Concepts (UK)	ProTAXX	No information[36]	§	0535 – Germany
Vasmed Technologies (United Arab Emirates)¶	Angstrom III	No information[37]	Jun 2008	No information
Simvastatin-eluting stent				
Iberhospitex (Spain)	Irist®	No information[38a/b/c]	§	0318 - Spain
Sirolimus-eluting stent				
Alvimedica Medical Technologies (Turkey)	Coracto	No information[39a/b]	§§	No information
Balton (Poland)	CARLO S®	No information	§§	No information
	PROLIM®	No information	§§	No information
	ALEX®	No information	§§	No information
CID (Italy)*	Cre8™	No information[40]	Jul 2011	0373 – Italy
Cordis (USA)**	CYPHER®	*De novo* and restenotic coronary lesion	Apr 2002	No information
	CYPHER®	In-stent restenosis	Feb 2004	No information
	CYPHER® SELECT™	No information	? 2003	No information
	CYPHER® SELECT™	In-stent restenosis	Apr 2004	No information
	CYPHER® SELECT™	Severe claudication and critical limb ischaemia in infrapopliteal lesion[41]	Sep 2006	No information
	CYPHER® SELECT™ Plus	No information	Jun 2006	No information
	CYPHER® SELECT™ Plus	STEMI	Aug 2008	No information
	CYPHER® SELECT™ Plus	Diabetes mellitus[42]	Feb 2009	No information
Meryl Life Sciences (India)	BioMime™	No information[43]	Dec 2010	No information

Table 1. Overview of CE-marked DES (continued)

Manufacturer	Medical device	Indications for use	CE mark	Notified body
Sirolimus-eluting stent				
Sahajanand Medical Technologies (India)	Supralimus®	Patients with symptomatic ischemic heart disease due to coronary artery lesions with reference vessel diameter ≥2.25 mm to ≤4.00 mm[44]	Jun 2011	1293 – Slowak Rep.
	Supralimus-Core®	Patients with symptomatic ischemic heart disease due to coronary artery lesions with reference vessel diameter ≥2.5 mm to ≤3.5 mm[45]	Jun 2011	1293 – Slowak Rep.
MicroPort Medical (PR China)	FIREBIRD1	No information[46]	§§	No information
Translumina (Germany)	YUKON® Choice^{DES}	No information[47a/b]	Apr 2006[a]	0124 – Germany
Vascular Concepts (UK)	ProNOVA	No information[48]	§	0535 – Germany
Tacrolimus-eluting stent				
CID (Italy)*	Janus	No information	? 2003	No information
	Janus Flex™	No information[49a/b]	Oct 2004	0373 – Italy
	Janus Optima	No information[50a/b]	§	
	Janus Optima Jet	No information[51a/b]	Mar 2010	
Trapidil-eluting stent				
Clearstreaam Techologies Group (Ireland)	Intrepide™	No information[52]	Apr 2008	0344 – Netherlands
	Intrepide™	Diabetes mellitus	Apr 2009	0344 – Netherlands
Tretinoin-eluting stent				
Aachen Resonance (Germany)	Vita©	No information[15]	§	No information
Zotarolimus-eluting stent				
Medtronic Vascular (USA)	Endeavor®	No information	Jun 2005	No information
	Endeavor® Resolute	No information	Oct 2007	No information
	Endeavor®	ACS (NSTEMI, STEMI)	May 2009	No information
	Resolute Integrity	No information	Aug 2010	No information
	Resolute Integrity	Diabetes mellitus, multivessel disease, long lesion, small vessel[53]	? 2010	No information

Table 1. Overview of CE-marked DES (continued)

Abbreviations: ACS – acute coronary syndrome, BMS – bare metal stent, CAD – coronary artery disease, CE – Conformité Européenne, DES – drug-eluting stent, NSTEMI – non-ST-segment elevation myocardial infarction, STEMI – ST-segment elevation myocardial infarction

† XIENCE™ V also distributed by Boston Scientific Corp (USA) as PROMUS™.
†† PROMUS™ stent is a private-labelled XIENCE™ V stent; PROMUS license agreement will expire in mid-2012.
‡ Board of Directors approved Plan of Complete Liquidation and Dissolution of the Company (May 2009) and company made final distribution to stockholders (December 2009).
‡‡ Opto Circuits India Ltd (India) acquired Eurocor GmbH (Germany) in 2005.
¶ Vasmed Technologies Ltd (United Arab Emirates) is a subsidiary of Steripharm Ltd (India).
¶¶ Biosensors International Group Ltd (Singapore) acquired Devax Inc (USA) in October 2010.
* Sorin Biomedica Cardio Srl (Italy) sold cardiovascular division to CID Srl (Italy) in December 2008.
** Cordis Corporation (USA) announced (June 2011) it will stop manufacturing the CYPHER and CYPHER SELECT Plus by the end of 2011.
a Market launch of medical device.

§ No date of CE mark certification; CE mark depicted on manufacturer's website or in DES brochure.
§§ No date of CE mark certification; CE mark not depicted, only ordering information is available indicating that DES is placed on the market.

1 Stent length 8-11-14-18-23/24-28 mm, stent diameter 2.5-2.75-3.0-3.25-3.5-4.0 mm.
2 Stent length 8-11-14-18-23/24-28 mm, stent diameter 2.25 mm.
3 Stent length 33 and 36 mm, stent diameter range 2.5-3.5 mm.
4 Stent length 8-14-18-24-28 mm, stent diameter 2.5-3.0-3.5 mm.
5 NX36 allows for the deployment of one series of segments resulting in a customised stent implantation for the treatment of patients presenting one coronary lesion up to length of 36 mm.
6 NX60 allows for the deployment of up to two series of segments resulting in two subsequent customised stent implantations for the treatment of patients presenting one or two coronary lesions. The total or cumulative lesion length treatable is up to 60 mm.
7 Stent length 8-12-15-18-23-28 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.
8 Stent length ≤ 28 mm, stent diameter 2.25 mm.
9 XIENCE PRIME™: stent length 8-12-15-18-23-28 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.
XIENCE PRIME™ SV: stent length 8-12-15-18-23-28 mm, stent diameter 2.25 mm.
XIENCE PRIME™ LL: stent length 33-38 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.
10 PCR Online press release announced that manufacturer received CE mark [PCROnline, 2011]. See 9 for stent length and diameter.
11 Press release contained following information: 'In addition to the clinical trial product, ABSORB will be made available in select sizes to a limited number of centres in Europe later this year and into 2012. […] A full-scale European commercial launch of ABSORB with a broad size matrix is planned by the end of 2012.' [Abbot Vascular, 2011].
12 Stent length 8-12-15-18-23-28 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.
13 Boston's website contained following information: 'The PROMUS™ Everolimus Eluting Stent System is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete de novo native coronary artery lesions (length less than or equal to 28 mm) with a reference vessel diameter of 2.25 mm – 4.0 mm.'
14a PROMUS™ Element™: stent length 8-12-16-20-24-28-32 mm, stent diameter 2.25-2.5-2.75-3.0-3.5-4.0 mm.
14b PROMUS™ Element™ Long: stent length 38 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.
15 Stent length 10-13-15-18-21-24-27-30-33-36-39 mm, stent diameter 2.5-2.75-3.0-3.25-3.5-4.0 mm.

Table 1. Overview of CE-marked DES (continued)

[16a] Stent length 8-13-18-23-28-33 mm, stent diameter 2.75-3.0-3.25-3.5-4.0 mm.
[16b] Stent length 8-13-18-23 mm, stent diameter 2.5 mm.
[17a] Stent length 8-12-16-19 mm, balloon diameter 2.0-2.25-2.5-2.75 mm.
[17b] Stent length 10-14-18-18-24-28-38 mm, balloon diameter 3.0-3.25-3.5-4.0 mm.
[18] Stent length 8-10-12-15-18-22-25-29-34 mm, stent diameter 2.25-2.5-2.75-3.0-3.25-3.5-3.75-4.0-4.5 mm.
[19] Stent length 8-13-16-19-25-28-32 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.
[20] Stent length 8-12-15-18-23-28 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.
[21] Stent diameter 4.0-4.5-5.0 mm.
[22] Seven stent lengths, stent diameter 4.0 mm.
[23] Stent length 38 mm, stent diameter 2.75-3.0-3.5-4.0 mm.
[24] Press release contained following statement: 'As the results of the expanded CE mark, the TAXUS Liberté stent system in the European Union is indicated for the treatment of de novo and restenotic lesions or total occlusions in patients with coronary artery disease – angina; silent ischemia; acute myocardial infarction – to improve luminal diameter and reduce restenosis with the stent and at the stent edges in native coronary arteries. The TAXUS Liberté stent system is also indicated for patients with concomitant diabetes mellitus as well as treatment of abrupt or threatened closure in patients with failed interventional therapy.' [Boston Scientific Corporation, 2007].
[25] Stent length 12-16-20-24-28-32 mm, stent diameter 2.25-2.5-2.75-3.0-3.5-4.0-4.5 mm. Stent length 8 mm, stent diameter 2.25-2.5-2.75-3.0-3.5-4.0 mm. Stent length 38 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm. Press release contained following statement: 'This approval includes a specific indication for the treatment of diabetic patients' [Boston Scientific Corporation, 2010]. No further information on indications in press release.
[26] Treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 9 mm.
[27a] Stent length 8-10-13-16-18-23-28-33-38 mm, stent diameter 2.25-2.5-2.75-3.0-3.25-3.5-4.0 mm.
[27b] Stent length 13-16-18-23-28-33 mm, stent diameter 4.5-5.0-5.5-6.0 mm.
[28] Stent length 9-13-15-19-23-28-32 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.
[29] Stent length 8-12-15-18-21-28 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.
[30a] Stent length 9-14-19 mm, stent diameter 2.0-2.25 mm.
[30b] Stent length 9-14-19-23-28 mm, stent diameter 2.5-2.75 mm.
[30c] Stent length 14-18-23-28-36 mm, stent diameter 3.0-3.5 mm.
[31] Stent length 10-14-18-24-28-38 mm, balloon diameter 2.0-2.25-2.5-2.75-3.0-3.25-3.5-4.0 mm.
[32] Main branch catheter 2.5-3.0-3.5, side branch catheter 2.0-2.5-3.0 mm, stent length 18 mm.
[33] Side branch catheter 2.5-3.0 mm, stent length 8 mm.
[34] Stent length 8-12-16-20-24 mm, stent diameter 2.25-2.5-2.75-3.0-3.5-4.0 mm.
[35] Stent length 11-16-19-23-29-33-39 mm, stent diameter 2.25-2.5-2.75-3.0-3.5-4.0 mm.
[36] Stent length 8-10-13-16-18-23-28-33 mm, stent diameter 2.5-2.75-3.0-3.25-3.5-4.0-4.5-5.0-5.5-6.0 mm.
[37] Stent length 10-13-15-18-21-24-27-30-33-36-39 mm, stent diameter 2.5-2.75-3.0-3.25-3.5-4.0 mm.
[38a] Stent length 9-14-19-23-28-36 mm, stent diameter 2.5-2.75 mm (Irist® Small).
[38b] Stent length 9-14-18-23-28-36 mm, stent diameter 3.0-3.5-4.0 mm.
[38c] Stent length 14-18-23-28-36 mm, stent diameter 4.0-4.5 mm.
[39a] Stent length 9-13-17-21-24-28 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.
[39b] Stent length 9-13-17-21-24-28-32 mm, stent diameter 3.0-3.5-4.0 mm.

Table 1. Overview of CE-marked DES (continued)

[40] Stent length 12-16-20-25 mm, stent diameter 2.5-2.75-3.0-3.5-4.0-4.5 mm. Stent length 31 mm, stent diameter 3.0-3.5-4.0-4.5 mm.

[41] TCTMD Industry News Letter contained following information: 'The CYPHER SELECT® Sirolimus-eluting Stent received the CE Mark in Europe for use in the treatment of severe claudication and critical limb ischemia (CLI) of infrapopliteal lesions, which is the most severe form of arterial disease in the leg. The CYPHER SELECT® Sirolimus-eluting Stent is the first drug-eluting stent to obtain CE approval for severe claudication and critical limb ischemia (CLI) that is associated with infrapopliteal lesions.' [TCTMD, 2006].

[42] TCTMD Industry News Letter contained following information: 'In addition to diabetes, CYPHER SELECT® Plus Stent has recently received CE marking for the following coronary conditions: chronic total occlusion, multi-vessel disease and bifurcations. In August 2008, CYPHER SELECT® Plus received CE marking for the treatment of acute myocardial infarction (heart attack). CYPHER SELECT® Plus Stent was previously indicated for de novo lesions, in stent restenosis and small vessels. CYPHER SELECT® Plus has a total of eighteen different indications.' [TCTMD, 2009].

[43] Stent length 8-13-16-19-24-29-32-37-40 mm, stent diameter 2.5-2.75-3.0-3.5-4.0-4.5 mm. PCR Online press release announced that manufacturer received CE mark [PCROnline, 2010].

[44] Stent length 11-16-19-23-29-33-39 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.

[45] Stent length 8-12-16-20-24-28-32-36-40 mm, stent diameter 2.5-2.75-3.0-3.5 mm.

[46] Stent length 13-18-23-29-33 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.

[47a] Stent length 8-12-16-18-21-24-28-32 mm, balloon diameter 2.0-2.25-2.5 mm.

[47b] Stent length 8-12-16-18-21-24-28-32-40 mm, balloon diameter 2.5-2.75-3.0-3.5-4.0 mm.

[48] Stent length 13-18-23-28-33-38 mm, stent diameter 2.25-2.5-2.75-3.0-3.25-3.5-4.0 mm.

[49a] Stent length 12-15-19-25 mm, stent diameter 2.5-2.75 mm.

[49b] Stent length 12-15-19-25-31 mm, stent diameter 3.0-3.5-4.0 mm.

[50a] Stent length 12-15-19-25 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.

[50b] Stent length 31 mm, stent diameter 3.0-3.5-4.0 mm.

[51a] Stent length 12-15-19-25 mm, stent diameter 2.5-2.75-3.0-3.5-4.0 mm.

[51b] Stent length 31 mm, stent diameter 3.0-3.5-4.0 mm.

[52] Stent length 8-12-16-20-24-28-32 mm, inflated balloon diameter 2.5-2.75-3.0-3.5-4.0 mm

[53] Medtronic's website contained following information: 'Resolute Integrity DES has now expanded indications for diabetes mellitus, multivessel disease, long lesions and small vessels.' http://www.medtronicstents.com/en/en_resolute_integrity.html.

Appendix II FDA-approved DES

DES applications are assigned to the Center for Devices and Radiological Health for lead review with consultation provided by the Center for Drug Evaluation and Research. FDA reviewers examine all individual DES components (i.e., delivery system, stent platform, coating and drug) as well as the complete finished product. For several years, only two DES (CYPHER™, TAXUS™ Express²™) were approved in the USA (Table 2).

Table 2. Overview of FDA-approved DES

Manufacturer	Name of medical device	Indications for use	Approval
Everolimus-eluting stent			
Abbott Vascular (USA)	XIENCE™ V[†]	*De novo* lesion in native coronary artery[1]	Jul 2008
	XIENCE nano™	*De novo* lesion in native coronary artery[2]	May 2011
	XIENCE PRIME™[††]	*De novo* lesion in native coronary artery[3]	Nov 2011
Boston Scientific (USA)	PROMUS™	*De novo* lesion in native coronary artery[1]	Jul 2008
	PROMUS™	*De novo* lesion in native coronary artery[4]	May 2011
	PROMUS Element™	*De novo* lesion in native coronary artery[3]	Nov 2011
Paclitaxel-eluting stent			
Boston Scientific (USA)	TAXUS™ Express²™	*De novo* lesion in native coronary artery[5]	Mar 2004
	TAXUS™ Express²™	Restenotic lesion in BMS[6]	Sep 2008
	TAXUS™ Express²™	Large vessel[7]	-
	TAXUS™ Express²™ Atom™	Small vessel[6]	Sep 2008
	TAXUS® Liberté®	*De novo* lesion in native coronary artery[8]	Oct 2008
	TAXUS® Liberté® Atom™	*De novo* lesion in native coronary artery[9]	May 2009
	TAXUS® Liberté™ Long	*De novo* lesion in native coronary artery[10]	Jul 2009
	ION™ ¶	*De novo* lesion in native coronary artery[11]	Apr 2011
Sirolimus-eluting stent			
Cordis (USA)*	CYPHER™	*De novo* lesion in native coronary artery[12]	Apr 2003
	CYPHER®	Small vessel[13]	Sep 2009
	CYPHER®	Large vessel[14]	Feb 2011
Zotarolimus-eluting stent			
Medtronic Vascular (USA)	Endeavor®	*De novo* lesion in native coronary artery[15]	Feb 2008
	Endeavor® Sprint[‡]	*De novo* lesion in native coronary artery[15]	Oct 2008

Abbreviations: BMS – bare metal stent, DES – drug-eluting stent, FDA – Food and Drug Administration

[†] Also marketed by Boston Scientific Corp (USA) as PROMUS™.

[††] The XIENCE PRIME family of stent systems includes XIENCE PRIME (stent diameters 2.25, 2.5, 2.75, 3.0, 3.5 4.0 mm, stent lengths 8, 12, 15, 18, 23 mm) and XIENCE PRIME LL (stent diameters 2.5, 2.75, 3.0, 3.5, 4.0 mm, stent lengths 28, 33, 38 mm; stent diameter 2.25 mm, stent length 28 mm). Also marketed by Boston Scientific Corp (USA) as PROMUS Element™.

[‡] Endeavor® mounted on Sprinter™ balloon for rapid exchange.

¶ Outside the US, ION™ is commercialised as TAXUS® Element™.

* Cordis Corporation (USA) announced (June 2011) it will stop manufacturing the CYPHER by the end of 2011.

[1] Patient characteristics: symptomatic heart disease. Lesion characteristics: length ≤ 28 mm, reference vessel diameter ≥ 2.5 mm to ≤ 4.25 mm.

[2] Patient characteristics: symptomatic heart disease. Lesion characteristics: length ≤ 28 mm, reference vessel diameter ≥ 2.25 mm to < 2.50 mm.

[3] Patient characteristics: symptomatic heart disease. Lesion characteristics: length ≤ 32 mm, reference vessel diameter ≥ 2.25 mm to ≤ 4.25 mm.

Table 2. Overview of FDA-approved DES (continued)

[4] Patient characteristics: symptomatic heart disease. Lesion characteristics: length ≤ 28 mm, reference vessel diameter ≥ 2.25 mm to < 2.50 mm.
[5] Patient characteristics: none. Lesion characteristics: length ≤ 28 mm, reference vessel diameter ≥ 2.5 mm to ≤ 3.75 mm.
[6] Available at: http://bostonscientific.mediaroom.com/index.php?s=43&item=768
[7] Lesion characteristics: reference vessel diameter 4.0 mm.
[8] Patient characteristics: none. Lesion characteristics: length ≤ 28 mm, reference vessel diameter ≥ 2.5 mm to ≤ 4.0 mm.
[9] Patient characteristics: none. Lesion characteristics: length ≤ 28 mm, reference vessel diameter ≥ 2.25 mm to < 2.5 mm.
[10] Patient characteristics: none. Lesion characteristics: length ≤ 34 mm, reference vessel diameter ≥ 2.75 mm to ≤ 4.0 mm.
[11] Patient characteristics: none. Lesion characteristics: length ≤ 34 mm, reference vessel diameter ≥ 2.25 mm to ≤ 4.00 mm.
[12] Patient characteristics: symptomatic ischaemia. Lesion characteristics: length ≤ 30 mm, reference vessel diameter ≥ 2.5 mm to ≤ 3.5 mm.
[13] Lesion characteristics: reference vessel diameter ≥ 2.25 mm to < 2.5 mm.
[14] Lesion characteristics: reference vessel diameter > 3.5 mm to ≤ 4.0 mm.
[15] Patient characteristics: symptomatic heart disease. Lesion characteristics: length ≤ 27 mm, reference vessel diameter ≥ 2.5 mm to ≤ 3.5 mm.

Appendix III Clinical outcomes of DES

Table 3. Death and myocardial infarction from observational studies

			Hazard ratio, odds ratio[1], relative risk[2] (95% confidence interval)	
Reference	Follow-up (year)	Comparison of stent type	Death	Myocardial infarction
Off-label use of DES vs on-label use of DES				
Beohar et al. [2007]	1	(SES PES) vs (SES PES)[#]	1.34 (0.94-1.92)	1.16 (0.75-1.79)
Beohar et al. [2007]	1	(SES PES) vs (SES PES)[¶]	1.14 (0.72-1.79)	0.81 (0.48-1.40)
Quasim et al. [2007]	1	(SES PES) vs (SES PES)	-	-
Win et al. [2007]	1	(SES PES) vs (SES PES)	1.36 (0.85-2.17)	2.20 (1.68-2.89)
Brodie et al. [2008]	2	(SES PES) vs (SES PES)	1.29 (1.04-1.60)	1.37 (1.05-1.77)
Jeremias et al. [2008]	1	SES vs SES	-	-
Bezerra et al. [2010]	1	SES vs SES	1.6 (0.89-2.98)	1.7 (0.77-3.70)
Ahmed et al. [2008]	1	PES vs PES	-	-
Lasala et al. [2009a]	2	PES vs PES	-	-
Lasala et al. [2009b]	2	PES vs PES		
Flores et al. [2008]	2.8	PES vs PES	1.6 (0.8-3.5)	2.1 (0.9-4.9)
Latib et al. [2009]	1	EES vs EES	-	-
Lotan et al. [2009]	1	ZES vs ZES	-	-
Meredith et al. [2011]	2	ZES vs ZES	-	-
Off-label use of DES vs off-label use of BMS				
Applegate et al. [2008a]	1	(SES PES) vs BMS	0.72 (0.54-0.94)	
Marroquin et al. [2008]	1	(SES PES) vs BMS	0.94 (0.64-1.38)	0.71 (0.50-1.00)
Roy et al. [2008b]	1	(SES PES) vs BMS	-	-
Austin et al. [2008]	2	(SES PES) vs BMS	0.63 (0.40-0.99)	1.02 (0.69-1.54)
Brodie et al. [2008]	2	(SES PES) vs BMS	0.54 (0.42-0.70)	0.62 (0.45-0.86)
Harjai et al. [2008]		(SES PES) vs BMS	0.63 (0.39-1.03)	-
Ko et al. [2009]	3	(SES PES) vs BMS	-	-
Carlsson et al. [2009]	4	(SES PES) vs BMS	0.96 (0.86-1.08)[2]	1.00 (0.87-1.14)[2]
Harjai et al. [2009]	4	(SES PES) vs BMS	-	-
Gao et al. [2009]	2	(SES PES ZES) vs BMS	0.57 (0.28-1.19)	0.65 (0.35-1.21)
Off-label use of DES vs off-label use of DES				
Ruperto et al. [2009]	3	SES vs PES	0.93 (0.47-1.83)	0.46 (0.19-1.13)
Unrestricted use of DES vs unrestricted use of BMS				
Lemos et al. [2004b]	1	SES vs BMS	0.78 (0.41-1.52)	
Ong et al. [2006]	2	SES vs BMS	0.92 (0.55-1.54)	
Kaltoft et al. [2009]	2	SES vs BMS	0.73 (0.83-1.07)[2]	1.15 (0.91-1.47)[2]
Daemen et al. [2006]	3	SES vs BMS	1.09 (0.71-1.45)	
Jensen et al. [2010]	3	SES vs BMS	0.90 (0.76-1.06)[2]	1.23 (1.00-1.51)[2]
Daemen et al. [2008]	4	SES vs BMS	0.88 (0.59-1.31)	-
Daemen et al. [2009]	4	SES vs BMS	-	-
Simsek et al. [2010b]	4	SES vs BMS	0.87 (0.57-1.34)	
Simsek et al. [2010a]	6	SES vs BMS	1.00 (0.85-1.18)	
Kaltoft et al. [2009]	2	PES vs BMS	1.03 (0.82-1.28)[2]	1.38 (1.06-1.81)[2]
Jensen et al. [2010]	3	PES vs BMS	1.02 (0.84-1.23)[2]	1.38 (1.09-1.74)[2]
Daemen et al. [2009]	4	PES vs BMS	-	-
Simsek et al. [2010b]	4	PES vs BMS	1.09 (0.80-1.50)	
Simsek et al. [2010a]	6	PES vs BMS	0.97 (0.82-1.15)	

Table 3. Death and myocardial infarction from observational studies (continued)

Reference	Follow-up (year)	Comparison of stent type	Hazard ratio, odds ratio[1], relative risk[2] (95% confidence interval) Death	Myocardial infarction
Unrestricted use of DES vs unrestricted use of BMS				
Williams et al. [2006]	1	(SES PES) vs BMS	-	-
Abbott et al. [2007]	1	(SES PES) vs BMS	0.97 (0.66-1.43)	1.02 (0.73-1.43)
Nienaber et al. [2009]	1	(SES PES) vs BMS	-	-
Jensen et al. [2007]	1¼	(SES PES) vs BMS	0.90 (0.75-1.09)	4.00 (2.06-7.79)
Marzocchi et al. [2007]	2	(SES PES) vs BMS	0.90 (0.72-1.13)	0.91 (0.72-1.16)
Tu et al. [2007]	2	(SES PES) vs BMS	-	-
Applegate et al. [2008a]	2	(SES PES) vs BMS	0.71 (0.54-0.92)	
Mauri et al. [2008]	2	(SES PES) vs BMS	-	-
Alahmar et al. [2009]	2	(SES PES) vs BMS	-	
Kaltoft et al. [2009]	2	(SES PES) vs BMS	0.97 (0.83-1.13)[2]	1.24 (1.02-1.51)[2]
Auer et al. [2010]	2.7	(SES PES) vs BMS	0.91 (0.76-1.11)	1.11 (0.91-1.29)
Lagerqvist et al. [2007]	3	(SES PES) vs BMS	1.18 (1.04-1.35)[2]	-
Tu et al. [2007]	3	(SES PES) vs BMS	-	
Applegate et al. [2009]	3	(SES PES) vs BMS	0.80 (0.64-1.01)	
Jensen et al. [2010]	3	(SES PES) vs BMS	0.94 (0.82-1.08)[2]	1.29 (1.08-1.52)[2]
Applegate et al. [2008b]	4	(SES PES) vs BMS		
Daemen et al. [2009]	4	(SES PES) vs BMS	1.10 (0.90-1.34)	0.75 (0.57-0.98)
Harjai et al. [2009]	4	(SES PES) vs BMS	0.71 (0.51-0.98)	1.22 (0.84-1.75)
Yan et al. [2008]	1	DES vs BMS	0.73 (0.52-1.04)[1]	1.13 (0.79-1.62)[1]
Shishehbor et al. [2008]	4½	DES vs BMS	0.54 (0.45-0.66)	
Onuma et al. [2009]	½	EES vs BMS	0.51 (0.25-1.03)	
Gao et al. [2009]	2	(SES PES ZES) vs BMS	0.64 (0.35-1.16)	0.75 (0.45-1.26)
James et al. [2009]	5	(SES PES ZES) vs BMS	0.94 (0.85-1.05)	0.97 (0.88-1.06)
Bental et al. [2010]	5	(SES PES ZES EES other DES) vs BMS	0.75 (0.62-0.92)	-

Abbreviations: BMS – bare metal stent, DES – drug-eluting stent, EES – everolimus-eluting stent, PES – paclitaxel-eluting stent, SES – sirolimus-eluting stent, ZES – zotarolimus-eluting stent

[#] Off-label use vs standard use. Based on the information for use, off-label use for the SES was defined as stenting of a restenotic lesion, lesion in a bypass graft, lesion length greater than 30 mm or reference vessel diameter less than 2.5 mm or greater than 3.5 mm. For the PES, the lesion criteria were identical except for lesion length greater than 28 mm and reference vessel diameter less than 2.5 mm or greater than 3.75 mm.

[¶] Untested use vs standard use. Untested use was defined by the information for use that stated that the safety and effectiveness has not been established for the treatment of left main, ostial, bifurcation or totally occluded lesions.

Outcomes of studies reported as (cumulative) event rates instead of hazard ratio, odds ratio or relative risk denoted with -.

Table 4. Stent thrombosis from observational studies

			Hazard ratio, odds ratio[1], relative risk[2] (95% confidence interval)		
Reference	Follow-up (year)	Comparison of stent type	Definite ST Definite/probable ST[†]	Late ST (31 days – 1 year)	Very late ST (> 1 year)
Off-label use of DES vs on-label use of DES					
Beohar et al. [2007]	1	(SES PES) vs (SES PES)[#]	2.05 (0.82-5.14)[†]		
Beohar et al. [2007]	1	(SES PES) vs (SES PES)[¶]	3.17 (1.26-7.97)[†]		
Quasim et al. [2007]	1	(SES PES) vs (SES PES)	-[†]	-[†]	
Win et al. [2007]	1	(SES PES) vs (SES PES)	2.29 (1.02-5.16)[‡]		
Brodie et al. [2008]	2	(SES PES) vs (SES PES)	1.59 (0.97-2.61)[†]		
Jeremias et al. [2008]	1	SES vs SES		-[‡]	
Bezerra et al. [2010]	1	SES vs SES	2.9 (1.09-7.73)[1†]	8.4 (1.08-64.82)[1†]	
Ahmed et al. [2008]	1	PES vs PES	-[†]		
Lasala et al. [2009a]	2	PES vs PES			
Lasala et al. [2009b]	2	PES vs PES	-[†]	-[†]	-[†]
Flores et al. [2008]	2.8	PES vs PES			
Latib et al. [2009]	1	EES vs EES	-/-[†]	-	
Lotan et al. [2009]	1	ZES vs ZES	-/-[†]	-/-[†]	
Meredith et al. [2011]	2	ZES vs ZES	-[†]	-[†]	-[†]
Off-label use of DES vs off-label use of BMS					
Applegate et al. [2008a]	1	(SES PES) vs BMS	0.91 (0.46-1.80)[†]		-[†]
Marroquin et al. [2008]	1	(SES PES) vs BMS			
Roy et al. [2008b]	1	(SES PES) vs BMS			
Austin et al. [2008]	2	(SES PES) vs BMS			
Brodie et al. [2008]	2	(SES PES) vs BMS	0.65 (0.36-1.18)[†]		
Harjai et al. [2008]		(SES PES) vs BMS	1.13 (0.55-2.30)[†]		
Ko et al. [2009]	3	(SES PES) vs BMS			
Carlsson et al. [2009]	4	(SES PES) vs BMS			
Harjai et al. [2009]	4	(SES PES) vs BMS	-[†]		
Gao et al. [2009]	2	(SES PES ZES) vs BMS	0.40 (0.14-1.14)[†]		
Off-label use of DES vs off-label use of DES					
Ruperto et al. [2009]	3	SES vs PES	-	-	
Unrestricted use of DES vs unrestricted use of BMS					
Lemos et al. [2004b]	1	SES vs BMS			
Ong et al. [2006]	2	SES vs BMS			
Kaltoft et al. [2009]	2	SES vs BMS	0.61 (0.33-1.11)[2]	0.63 (0.18-2.17)[2]	-
Daemen et al. [2006]	3	SES vs BMS			
Jensen et al. [2010]	3	SES vs BMS	0.72 (0.42-1.22)[2]	-	2.31 (1.01-5.32)[2]
Daemen et al. [2008]	4	SES vs BMS	0.97 (0.41-2.29)	-	-
Daemen et al. [2009]	4	SES vs BMS	-		
Simsek et al. [2010b]	4	SES vs BMS	-	-	-
Simsek et al. [2010a]	6	SES vs BMS	-	-	-
Kaltoft et al. [2009]	2	PES vs BMS	1.75 (1.09-2.82)[2]	4.84 (2.35-10.0)[2]	-
Jensen et al. [2010]	3	PES vs BMS	2.06 (1.33-3.19)[2]	3.25 (1.20-8.79)[2]	4.23 (1.97-9.09)[2]
Daemen et al. [2009]	4	PES vs BMS	-		
Simsek et al. [2010b]	4	PES vs BMS	-	-	-
Simsek et al. [2010a]	6	PES vs BMS	-	-	-

Table 4. Stent thrombosis from observational studies (continued)

Reference	Follow-up (year)	Comparison of stent type	Hazard ratio, odds ratio[1], relative risk[2] (95% confidence interval) Definite ST, Definite/probable ST[†]	Late ST (31 days – 1 year)	Very late ST (> 1 year)
Unrestricted use of DES vs unrestricted use of BMS					
Williams et al. [2006]	1	(SES PES) vs BMS	-[†]		
Abbott et al. [2007]	1	(SES PES) vs BMS	-		
Nienaber et al. [2009]	1	(SES PES) vs BMS	-		
Jensen et al. [2007]	1¼	(SES PES) vs BMS	0.93 (0.60-1.46)	0.93 (0.35-2.89)	10.93 (1.27-93.76)
Marzocchi et al. [2007]	2	(SES PES) vs BMS	-	-[§]	-[§§]
Tu et al. [2007]	2	(SES PES) vs BMS			
Applegate et al. [2008a]	2	(SES PES) vs BMS	0.97 (0.49-1.91)[†]		
Mauri et al. [2008]	2	(SES PES) vs BMS			
Alahmar et al. [2009]	2	(SES PES) vs BMS	-/-[†]	-[††]	-[††]
Kaltoft et al. [2009]	2	(SES PES) vs BMS	1.07 (0.71-1.61)[2]	0.98 (0.34-2.82)[2]	5.15 (1.81-14.69)[2]
Auer et al. [2010]	2.7	(SES PES) vs BMS	-	-	83.3 (0.97-166)
Lagerqvist et al. [2007]	3	(SES PES) vs BMS			
Tu et al. [2007]	3	(SES PES) vs BMS			
Applegate et al. [2009]	3	(SES PES) vs BMS	1.07 (0.57-2.01)		
Jensen et al. [2010]	3	(SES PES) vs BMS	1.24 (0.85-1.81)[2]		2.89 (1.48-5.65)[2]
Applegate et al. [2008b]	4	(SES PES) vs BMS	-/-[†]	0.07 (0.01-0.55)[1]	3.50 (0.76-16.24)[1]
				0.17 (0.05-0.58)[1†]	1.71 (0.59-4.94)[1†]
Daemen et al. [2009]	4	(SES PES) vs BMS	1.26 (0.82-1.95)	-	-
Harjai et al. [2009]	4	(SES PES) vs BMS	1.56 (0.86-2.86)[†]		
Yan et al. [2008]	1	DES vs BMS		0.85 (0.41-1.76)[1††]	
Shishehbor et al. [2008]	4½	DES vs BMS			
Onuma et al. [2009]	½	EES vs BMS	-	-[§]	
Gao et al. [2009]	2	(SES PES ZES) vs BMS	-	-[††]	-[††]
			0.94 (0.46-1.92)[†]		
James et al. [2009]	5	(SES PES ZES) vs BMS			
Bental et al. [2010]	5	(SES PES ZES EES other DES) vs BMS			

Abbreviations: BMS – bare metal stent, DES – drug-eluting stent, EES – everolimus-eluting stent, PES – paclitaxel-eluting stent, SES – sirolimus-eluting stent, ST – stent thrombosis, ZES – zotarolimus-eluting stent

[#] Off-label use vs standard use. Based on the information for use, off-label use for the SES was defined as stenting of a restenotic lesion, lesion in a bypass graft, lesion length greater than 30 mm or reference vessel diameter less than 2.5 mm or greater than 3.5 mm. For the PES, the lesion criteria were identical except for lesion length greater than 28 mm and reference vessel diameter less than 2.5 mm or greater than 3.75 mm.

[¶] Untested use vs standard use. Untested use was defined by the information for use that stated that the safety and effectiveness has not been established for the treatment of left main, ostial, bifurcation, or totally occluded lesions.

Outcomes of studies reported as (cumulative) event rates instead of hazard ratio, odds ratio or relative risk denoted with -.

[†] Definite/probable stent thrombosis.

[††] Definite/probable/possible stent thrombosis.

[‡] Stent thrombosis not defined as definite, definite/probable, or definite/probable/possible.

[§] Late stent thrombosis: 30 days to 6 months.

[§§] Very late stent thrombosis: > 6 months.

Table 5. Target vessel revascularization from observational studies

Reference	Follow-up (year)	Comparison of stent type	Hazard ratio, odds ratio[1] (95% confidence interval) Target vessel revascularization
Off-label use of DES vs on-label use of DES			
Beohar et al. [2007]	1	(SES PES) vs (SES PES)[#]	1.49 (1.13-1.98)
Beohar et al. [2007]	1	(SES PES) vs (SES PES)[¶]	1.49 (1.10-2.02)
Quasim et al. [2007]	1	(SES PES) vs (SES PES)	-
Win et al. [2007]	1	(SES PES) vs (SES PES)	
Brodie et al. [2008]	2	(SES PES) vs (SES PES)	1.87 (1.55-2.24)
Jeremias et al. [2008]	1	SES vs SES	-
Bezerra et al. [2010]	1	SES vs SES	0.9 (0.56-1.59)[1]
Ahmed et al. [2008]	1	PES vs PES	-
Lasala et al. [2009a]	2	PES vs PES	
Lasala et al. [2009b]	2	PES vs PES	
Flores et al. [2008]	2.8	PES vs PES	1.5 (0.7-3)
Latib et al. [2009]	1	EES vs EES	-
Lotan et al. [2009]	1	ZES vs ZES	-
Meredith et al. [2011]	2	ZES vs ZES	-
Off-label use of DES vs off-label use of BMS			
Applegate et al. [2008a]	1	(SES PES) vs BMS	0.67 (0.50-0.88)
Marroquin et al. [2008]	1	(SES PES) vs BMS	0.63 (0.52-0.77)
Roy et al. [2008b]	1	(SES PES) vs BMS	-
Austin et al. [2008]	2	(SES PES) vs BMS	0.67 (0.49-0.92)
Brodie et al. [2008]	2	(SES PES) vs BMS	0.61 (0.48-0.77)
Harjai et al. [2008]		(SES PES) vs BMS	0.35 (0.23-0.51)
Ko et al. [2009]	3	(SES PES) vs BMS	-
Carlsson et al. [2009]	4	(SES PES) vs BMS	
Harjai et al. [2009]	4	(SES PES) vs BMS	0.58 (0.39-0.85)
Gao et al. [2009]	2	(SES PES ZES) vs BMS	0.47 (0.33-0.68)
Off-label use of DES vs off-label use of DES			
Ruperto et al. [2009]	3	SES vs PES	1.07 (0.78-1.46)
Unrestricted use of DES vs unrestricted use of BMS			
Lemos et al. [2004b]	1	SES vs BMS	0.35 (0.21-0.57)
Ong et al. [2006]	2	SES vs BMS	0.53 (0.36-0.79)
Kaltoft et al. [2009]	2	SES vs BMS	
Daemen et al. [2006]	3	SES vs BMS	0.54 (0.37-0.78)
Jensen et al. [2010]	3	SES vs BMS	
Daemen et al. [2008]	4	SES vs BMS	0.57 (0.39-0.83)
Daemen et al. [2009]	4	SES vs BMS	-
Simsek et al. [2010b]	4	SES vs BMS	0.53 (0.37-0.75)
Simsek et al. [2010a]	6	SES vs BMS	0.81 (0.68-0.96)
Kaltoft et al. [2009]	2	PES vs BMS	
Jensen et al. [2010]	3	PES vs BMS	
Daemen et al. [2009]	4	PES vs BMS	-
Simsek et al. [2010b]	4	PES vs BMS	0.71 (0.62-0.81)
Simsek et al. [2010a]	6	PES vs BMS	0.81 (0.68-0.96)

Table 5. Target vessel revascularization from observational studies (continued)

Reference	Follow-up (year)	Comparison of stent type	Hazard ratio, odds ratio[1] (95% confidence interval) Target vessel revascularization
Unrestricted use of DES vs unrestricted use of BMS			
Williams et al. [2006]	1	(SES PES) vs BMS	0.58 (0.40-0.83)
Abbott et al. [2007]	1	(SES PES) vs BMS	-
Nienaber et al. [2009]	1	(SES PES) vs BMS	-
Jensen et al. [2007]	1¼	(SES PES) vs BMS	
Marzocchi et al. [2007]	2	(SES PES) vs BMS	0.68 (0.57-0.80)
Tu et al. [2007]	2	(SES PES) vs BMS	-
Applegate et al. [2008a]	2	(SES PES) vs BMS	0.62 (0.48-0.80)
Mauri et al. [2008]	2	(SES PES) vs BMS	-
Alahmar et al. [2009]	2	(SES PES) vs BMS	
Kaltoft et al. [2009]	2	(SES PES) vs BMS	
Auer et al. [2010]	2.7	(SES PES) vs BMS	
Lagerqvist et al. [2007]	3	(SES PES) vs BMS	
Tu et al. [2007]	3	(SES PES) vs BMS	
Applegate et al. [2009]	3	(SES PES) vs BMS	0.65 (0.51-0.82)
Jensen et al. [2010]	3	(SES PES) vs BMS	
Applegate et al. [2008b]	4	(SES PES) vs BMS	
Daemen et al. [2009]	4	(SES PES) vs BMS	0.69 (0.58-0.82)
Harjai et al. [2009]	4	(SES PES) vs BMS	
Yan et al. [2008]	1	DES vs BMS	0.87 (0.64-1.17)[1]
Shishehbor et al. [2008]	4½	DES vs BMS	
Onuma et al. [2009]	½	EES vs BMS	0.50 (0.27-0.90)
Gao et al. [2009]	2	(SES PES ZES) vs BMS	0.54 (0.40-0.74)
James et al. [2009]	5	(SES PES ZES) vs BMS	
Bental et al. [2010]	5	(SES PES ZES EES other DES) vs BMS	0.65 (0.53-0.80)

Abbreviations: BMS – bare metal stent, DES – drug-eluting stent, EES – everolimus-eluting stent, PES – paclitaxel-eluting stent, SES – sirolimus-eluting stent, ZES – zotarolimus-eluting stent

[#] Off-label use vs standard use. Based on the information for use, off-label use for the SES was defined as stenting of a restenotic lesion, lesion in a bypass graft, lesion length greater than 30 mm, or reference vessel diameter less than 2.5 mm or greater than 3.5 mm. For the PES, the lesion criteria were identical except for lesion length greater than 28 mm and reference vessel diameter less than 2.5 mm or greater than 3.75 mm.

[¶] Untested use vs standard use. Untested use was defined by the information for use that stated that the safety and effectiveness has not been established for the treatment of left main, ostial, bifurcation or totally occluded lesions.

Outcomes of studies reported as (cumulative) event rates instead of hazard ratio, odds ratio or relative risk denoted with -.

Table 6. Death and myocardial infarction of new-generation DES

Reference	Follow-up (year)	Comparison of stent type	Hazard ratio, rate ratio[1], relative risk[2] (95% confidence interval) Death	Myocardial infarction
Unrestricted use of BES vs unrestricted use of first-generation DES				
Windecker et al. [2008]	¾	BES vs SES	0.91 (0.51-1.62)[1]	1.25 (0.82-1.92)[1]
Wykrzykowska et al. [2011]	3	BES vs SES	-	1.01 (0.70-1.44)
Stefanini et al. [2011]	4	BES vs SES	0.89 (0.66-1.21)[1]	0.96 (0.69-1.33)[1]
Unrestricted use of EES vs unrestricted use of first-generation DES				
Onuma et al. [2009]	½	EES vs SES	0.87 (0.39-1.92)	
Mahmoudi et al. [2011]	1	EES vs SES	1.0 (0.56-1.7)	
Räber et al. [2011]	3	EES vs SES	0.92 (0.68-1.25)	0.62 (0.42-0.92)
Onuma et al. [2009]	½	EES vs PES	0.99 (0.52-1.89)	
Kehdi et al. [2010]	1	EES vs PES	1.21 (0.61-2.38)[2]	0.52 (0.33-0.84)[2]
Mahmoudi et al. [2011]	1	EES vs PES	1.2 (0.69-2.1)	
Smits et al. [2011]	2	EES vs PES	1.12 (0.67-1.87)[2]	0.52 (0.35-0.77)[2]
Unrestricted use of ZES vs unrestricted use of first-generation DES				
Park et al. [2010]	1	ZES[#] vs SES	-	-
Rasmussen et al. [2010]	1½	ZES[#] vs SES	1.61 (1.03-2.50)	2.22 (1.09-4.53)
Park et al. [2010]	1	ZES[#] vs PES	-	-
Unrestricted use of ZES vs unrestricted use of new-generation DES				
Serruys et al. [2010]	1	ZES[¶] vs EES	-	-
Silber et al. [2011]	2	ZES[¶] vs EES	-	-

Abbreviations: BES – biolimus-eluting stent, DES – drug-eluting stent, EES – everolimus-eluting stent, PES – paclitaxel-eluting stent, SES – sirolimus-eluting stent, ZES – zotarolimus-eluting stent

[#] Endeavor stent releases zotarolimus from a phopshorylcholine polymer.

[¶] Endeavor Resolute stent uses the same medicinal substance and a slightly modified Endeavor stent platform but a different polymer (BioLinx™ polymer system), which allows for a more extended release of zotarolimus.

Outcomes of studies reported as (cumulative) event rates instead of hazard ratio or relative risk denoted with -.

Table 7. Stent thrombosis of new-generation DES

Reference	Follow-up (year)	Comparison of stent type	Hazard ratio, rate ratio[1], relative risk[2] (95% confidence interval) Definite ST, Definite/probable ST[†]	Late ST (31 days – 1 year)	Very late ST (> 1 year)
Unrestricted use of BES vs unrestricted use of first-generation DES					
Windecker et al. [2008]	¾	BES vs SES	0.93 (0.47-1.85)[1]	0.49 (0.09-2.70)[1§§]	
			1.15 (0.62-2.12)[1†]	0.99 (0.25-3.96)[1†§§]	
Wykrzykowska et al. [2011]	3	BES vs SES	0.78 (0.43-1.43)		
Stefanini et al. [2011]	4	BES vs SES	0.62 (0.35-1.08)[1]	0.74 (0.17-3.33)[1]	0.20 (0.06-0.67)[1]
			0.73 (0.45-1.19)[1†]	1.24 (0.33-4.63)[1†]	0.29 (0.12-0.73)[1†]
Unrestricted use of EES vs unrestricted use of first-generation DES					
Onuma et al. [2009]	½	EES vs SES	-	-[§]	
Mahmoudi et al. [2011]	1	EES vs SES	-		
Räber et al. [2011]	3	EES vs SES	0.30 (0.12-0.75)	0.50 (0.09-2.73)	0.07 (0-1.16)[2*]
			0.64 (0.41-0.98)[†]	0.50 (0.09-2.73)[†]	0.07 (0-1.16)[2†*]
Onuma et al. [2009]	½	EES vs PES	-	-[§]	
Kehdi et al. [2010]	1	EES vs PES	0.22 (0.08-0.66)[2]	0.50 (0.25-1.67)[2§§§]	
			0.26 (0.11-0.64)[2†]		
Mahmoudi et al. [2011]	1	EES vs PES	-		
Smits et al. [2011]	2	EES vs PES	0.21 (0.08-0.55)[2]		0.23 (0.07-0.81)[2†]
			0.23 (0.11-0.49)[2†]		
Unrestricted use of ZES vs unrestricted use of first-generation DES					
Park et al. [2010]	1	ZES[#] vs SES	-/-[†]	-/-[†]	
Rasmussen et al. [2010]	1½	ZES[#] vs SES	2.19 (0.83-5.77)		
Park et al. [2010]	1	ZES[#] vs PES	-/-[†]	-/-[†]	
Unrestricted use of new ZES vs unrestricted use of new-generation DES					
Serruys et al. [2010]	1	ZES[¶] vs EES	-/-[†]	-	
Silber et al. [2011]	2	ZES[¶] vs EES	-[†]	-[†]	-[†]

Abbreviations: BES – biolimus-eluting stent, DES – drug-eluting stent, EES – everolimus-eluting stent, PES – paclitaxel-eluting stent, SES – sirolimus-eluting stent, ST – stent thrombosis, ZES – zotarolimus-eluting stent

[#] Endeavor stent releases zotarolimus from a phopshorylcholine polymer.

[¶] Endeavor Resolute stent uses the same medicinal substance and a slightly modified Endeavor stent platform but a different polymer (BioLinx™ polymer system), which allows for a more extended release of zotarolimus.

Outcomes of studies reported as (cumulative) event rates instead of hazard ratio or relative risk denoted with -.

[†] Definite/probable stent thrombosis.

[§] Late stent thrombosis: 30 days to 6 months.

[§§] Late stent thrombosis: 31 days to 9 months.

[§§§] Late stent thrombosis: 30 days to 1 year.

[*] Relative risks were calculated after a continuity correction of 0.5; p-values are from 2-sided Fisher exact test (very late definite ST p-value=0.007; very late definite/probable ST p-value=0.007).

Table 8. Target vessel revascularisation of new-generation DES

Reference	Follow-up (year)	Comparison of stent type	Hazard ratio, rate ratio[1], relative risk[2] (95% confidence interval) Target vessel revascularisation
Unrestricted use of BES vs unrestricted use of first-generation DES			
Windecker et al. [2008]	¾	BES vs SES	0.77 (0.53-1.13)[1]
Wykrzykowska et al. [2011]	3	BES vs SES	0.84 (0.62-1.13)
Stefanini et al. [2011]	4	BES vs SES	0.80 (0.63-1.03)[1]
Unrestricted use of EES vs unrestricted use of first-generation DES			
Onuma et al. [2009]	½	EES vs SES	1.45 (0.69-3.03)
Mahmoudi et al. [2011]	1	EES vs SES	1.3 (0.87-2.0)
Räber et al. [2011]	3	EES vs SES	0.75 (0.57-0.99)
Onuma et al. [2009]	½	EES vs PES	0.63 (0.35-1.12)
Kehdi et al. [2010]	1	EES vs PES	0.39 (0.24-0.64)[2]
Mahmoudi et al. [2011]	1	EES vs PES	1.1 (0.71-1.7)
Smits et al. [2011]	2	EES vs PES	0.41 (0.27-0.62)[2]
Unrestricted use of ZES vs unrestricted use of first-generation DES			
Park et al. [2010]	1	ZES[#] vs SES	-
Rasmussen et al. [2010]	1½	ZES[#] vs SES	2.42 (1.67-3.52)
Park et al. [2010]	1	ZES[#] vs PES	-
Unrestricted use of ZES vs unrestricted use of new-generation DES			
Serruys et al. [2010]	1	ZES[¶] vs EES	-
Silber et al. [2011]	2	ZES[¶] vs EES	-

Abbreviations: BES – biolimus-eluting stent, DES – drug-eluting stent, EES – everolimus-eluting stent, PES – paclitaxel-eluting stent, SES – sirolimus-eluting stent, ZES – zotarolimus-eluting stent

[#] Endeavor stent releases zotarolimus from a phopshorylcholine polymer.

[¶] Endeavor Resolute stent uses the same medicinal substance and a slightly modified Endeavor stent platform but a different polymer (BioLinx™ polymer system), which allows for a more extended release of zotarolimus.

Outcomes of studies reported as (cumulative) event rates instead of hazard ratio or relative risk denoted with -.

Appendix IV European clinical practice guidelines

Table 9. Classes of recommendations and levels of evidence for PCI indications

Indications	Class	Level
Patients with stable CAD [Silber et al., 2005][1]		
Routine stenting of *de novo* lesions in native coronary arteries	I	A
Routine stenting of *de novo* lesions in venous bypass grafts	I	A
Objective large ischaemia	I	A
High surgical risk, including left ventricular ejection fraction <35%	IIa	B
Chronic total occlusion[†]	IIa	C
Multi-vessel disease and/or diabetes mellitus[‡]	IIb/IIb	C/C
Unprotected left main coronary artery stenosis in the absence of other revascularisation options[¶]	IIb	C
Patients presenting with NSTE-ACS (NSTEMI) [Silber et al., 2005]		
Early PCI (<48 h) in patients with high-risk NSTE-ACS	I	A
Routine stenting in *de novo* lesions in all/high-risk patients with NSTE-ACS	I	C
Immediate PCI (<2.5 h) in patients with high-risk NSTE-ACS	IIa	B
Patients with persisting STE-ACS (STEMI) [Silber et al., 2005]		
Primary PCI in patients presenting <12 h after onset of chest pain/other symptoms and preferably up to 90 min after first medical contact; PCI should be performed by an experienced team	I	A
Routine stenting during primary PCI	I	A
Routine coronary angiography and PCI, if applicable, within 24 h after successful thrombolysis independent of angina and/or ischaemia	I	A
Rescue PCI in patients with failed thrombolysis within 40-60 min after starting administration	I	B
Ischaemia-driven PCI after successful thrombolysis	I	B
Primary PCI in patients with contraindications to thrombolysis	I	C
Primary PCI in patients presenting within 3-12 h after onset of chest pain/other symptoms	I	C
Emergency (multi-vessel) PCI in patients with cardiogenic shock in use with intra-aortic balloon pump even >12 to <36 h	I	C
Adjunctive medications for PCI [Silber et al., 2005]		
Acetylsalicylic acid in patients with stable CAD	I	B
Acetylsalicylic acid in patients with persisting STE-ACS (STEMI)	I	B
Acetylsalicylic acid in patients with NSTE-ACS	I	C
Clopidogrel administration for 6-12 months after DES implantation in patients with stable CAD	I	C
Acetylsalicylic acid plus clopidogrel administration for 9-12 months in patients with NSTE-ACS	I	B
Unfractionated heparin in patients with STE-ACS (STEMI)	I	C
Low-molecular weight heparins as replacement for unfractionated heparin in high-risk NSTE-ACS patients, if invasive strategy is not applicable	I	C
Adjunctive medications for PCI [Silber et al., 2005]		
Glycoprotein IIb/IIIa inhibitors immediately before PCI in high-risk NSTE-ACS	I	C
Glycoprotein IIb/IIIa inhibitors before diagnostic angiography and possible PCI with 48 h in high-risk NSTE-ACS	I	C
Glycoprotein IIb/IIIa inhibitors in high-risk NSTE-ACS with known coronary anatomy	I	C

Table 9. Classes of recommendations and levels of evidence for PCI indications (continued)

Indications	Class	Level
Glycoprotein IIb/IIIa inhibitors in patients with STE-ACS (STEMI) in all primary PCI	IIa	A
Glycoprotein IIb/IIIa inhibitors in stable CAD patients with complex lesions, threatening/actual closure, visible thrombus, no/slow reflow	IIa	C
Direct thrombin inhibitors to replace unfractionated heparin or low-molecular weight heparins in patients with heparin-induced thrombocytopenia	I	C
Direct thrombin inhibitors to replace unfractionated heparin or low-molecular weight heparins to reduce bleeding complications	IIa	C
Indications for DES [Silber et al., 2005]		
De novo lesions in native coronary arteries according to inclusion criteria	I	B
De novo long lesions in native coronary arteries according to inclusion criteria	I	B
Small vessels	IIa	C
Chronic total occlusions	IIa	C
Bifurcational/ostial lesions	IIa	C
Bypass stenoses	IIa	C
Insulin-dependent diabetes mellitus	IIa	C
Multi-vessel disease	IIa	C
Unprotected left main stenoses	IIa	C
In-stent restenoses	IIa	C
Patients with stable angina pectoris [Fox et al., 2006]		
PCI for single vessel disease technically suitable for percutaneous revascularisation in patients with moderate to severe symptoms not controlled by medical therapy in whom procedural risks do not outweigh potential benefits	I	A
PCI for single vessel disease technically suitable for percutaneous revascularisation in patients with mild to moderate symptoms which are nonetheless unacceptable to the patient, in whom procedural risks do not outweigh potential benefits	IIa	A
PCI for multi-vessel disease technically suitable for percutaneous revascularisation in patients with mild to moderate symptoms which are nonetheless unacceptable to the patient, in whom procedural risks do not outweigh potential benefits	IIa	A
Patients with stable and unstable coronary syndromes [Ryden et al., 2007]		
Diabetes mellitus[††]	IIa	B
Patients with NSTE-ACS [Bassand et al., 2007]		
Early (<72 h) coronary angiography followed by revascularisation (PCI or CABG) in patients with intermediate to high-risk features	I	A
PCI of non-significant lesions in not recommended	III	C
After critical evaluation of the risk-benefit ratio, and depending on known co-morbidities and potential need for non-cardiac surgery in the short/medium term (e.g., planned intervention or other conditions) requiring temporary withdrawal of dual antiplatelet therapy, consideration should be given to the type of stent to be implanted (BMS or DES)	I	C
Patients with persisting STE-ACS (STEMI) [Van de Werf et al., 2008]		
Primary PCI, preferred treatment if performed by an experienced team as soon as possible after first medical contact	I	A
Primary PCI, time from first medical contact to balloon inflation should be <2 h in any case and <90 min in patients presenting early (e.g., <2 h) with large infarct and low bleeding risk	I	B
Primary PCI, indicated for patients in shock and those with contraindications to fibrinolytic therapy irrespective of time delay	I	B
Rescue PCI, after failed fibrinolysis in patients with large infarcts if performed within 12 h after onset	IIa	A

Table 9. Classes of recommendations and levels of evidence for PCI indications (continued)

Abbreviations:
BMS – bare metal stent
CABG – coronary artery bypass graft
CAD – coronary artery disease. CAD involves two distinct processes: a fixed and barely reversible process that causes gradual luminal narrowing over decades (atherosclerosis) and a dynamic and potentially reversible process that punctuates the slow progression in a sudden and unpredictable way, causing rapid complete or partial coronary occlusion (thrombosis or vasospasm, or both). Generally, atherosclerosis predominates in lesions responsible for chronic stable angina, whereas thrombosis constitutes the critical component of culprit lesions responsible for acute coronary syndrome.
DES – drug-eluting stent
NSTE-ACS – non-ST-elevation acute coronary syndrome. In patients with rather persistent or transient ST-segment depression or T-wave inversion, flat T-waves, pseudo-normalisation of T-waves; or no ECG changes at presentation. The working diagnosis of NSTE-ACS is further qualified into NSTEMI or unstable angina.
NSTEMI – non-ST-segment elevation myocardial infarction
PCI – percutaneous coronary intervention
STE-ACS – ST-segment elevation acute coronary syndrome. Typically in patients with acute chest pain and persistent (>20 min) ST-segment elevation on the electrocardiogram, generally reflecting acute total coronary occlusion. Most of these patients will ultimately develop STEMI.
STEMI – ST-segment elevation myocardial infarction

[1] Assuming that the lesions considered most significant are technically suited for dilatation and stenting, the levels of recommendations refer to the use of stainless steel stents.
[†] The value of DES is currently under investigation.
[‡] Upcoming data on the use of DES in patients with multi-vessel disease and/or diabetes may change the situation.
[¶] Initial data on the use of DES seem promising.
[††] When PCI with stent implantation is performed, DES should be used.

Primary PCI is defined as intervention in the culprit vessel within 12 h after the onset of chest pain or other symptoms without prior (full or concomitant) thrombolytic or other clot-dissolving therapy.
Rescue PCI is defined as PCI in a coronary artery that remains occluded despite thrombolytic therapy.

National Insitute for Public Health
and the Environment
P.O. Box 1 | 3720 BA Bilthoven
www.rivm.com