REPORT OF THE ESC-EAPCI TASK FORCE ON THE EVALUATION OF CORONARY STENTS

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REVISION 1, 30 NOVEMBER 2014

Byrne RA, et al. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary.

European Heart Journal Oct 2015, 36 (38) 2608-2620; DOI: 10.1093/eurheartj/ehv203
http://eurheartj.oxfordjournals.org/content/ehj/36/38/2608.full.pdf

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CHAPTER 1: INTRODUCTION

Background

The European Society of Cardiology (ESC) has been asked in 2013 by the Clinical Investigation and Evaluation working group (CIE) (chaired by Dr Wolfgang Ecker), of the Medical Device Experts Group (MDEG, standing committee) of the European Commission to make recommendations for a revision of the EU medical device advisory document on the evaluation of coronary stents (MEDDEV 2.7.1., Appendix 1). These documents provide non-binding guidance including consensus statements and interpretative documents, which aim to ensure uniform application across Europe.

In order to revise the EU medical device advisory document on the evaluation of coronary stents (MEDDEV 2.7.1., Appendix 1), the ESC Task Force on Medical Devices under the leadership of Prof. Panos Vardas and Prof. Alan Fraser has delegated the task to the European Association of Percutaneous Cardiovascular Interventions (EAPCI) with the request to establish an expert advisory group in the field of percutaneous coronary intervention with specific expertise in the evaluation of coronary artery stents. As interventional cardiologists are the principal users of coronary artery stents, it was the responsibility of this Task Force to provide independent scientific expertise in the planning of the future approval process. It was the mission of the ESC-EAPCI Task Force to ensure priority to patient safety and protect patients from exposure to incompletely evaluated devices or devices without evidence of benefit while preserving expeditious access to innovative and novel devices.

The ESC-EAPCI Task Force has prospectively developed a work-plan reflected in the table of contents of this document with the aim to evaluate the need for common standards for the governance and clinical evaluation of coronary artery stents. The current document was prepared during four meetings (July 2013, December 2013, May 2014 and June 2014). As basis for this expert advisory document, the ESC-EAPCI Task Force established a comprehensive list of all drug-eluting coronary stents (DES) that have received a CE mark to date, which was provided for review to representatives of the European Notified Bodies (**Table 1**). In addition, the ESC-

EAPCI Task Force performed a systematic review of the literature of all published randomized clinical trials evaluating coronary artery stents between 2002 and 2013 (see **chapter 5**). Finally, the task force identified areas of unmet needs, which would benefit from innovative technologies to further improve outcomes of patients with symptomatic coronary artery disease.

The ESC-EAPCI Task Force engaged several stakeholders during the evaluation plan to obtain additional information including a representative of the US Food and Drug Administration as well as representatives of European regulators and Eucomed.

Task Force Members and Constitution

The following members constituted the ESC-EAPCI task force on the evaluation of coronary artery stents in Europe:

Chairman: Prof. Stephan Windecker

Co-chairman: Prof. Patrick Serruys

The representation of scientific societies and expertise within the ESC-EAPCI task force is summarized as follows:

- EAPCI representatives (Stephan Windecker - EAPCI President, Jean Fajadet - Past-President, Andreas Baumbach - Secretary, George Sianos Past Secretary, Javier Escaned – Treasurer, Past Secretary, Robert Byrne – Co-Chair, Scientific Documents)
- EuroPCR representative (William Wijns, Chairman)
- ESC Task Force Medical Devices (Stefan James, Stephan Windecker)
- ESC-EACTS Task Force on Myocardial Revascularisation (Stephan Windecker - Co-Chairman, Members Adnan Kastrati, Giulio Stefanini, Peter Jüni, William Wijns - past Co-chairman)
- CIE (Clinical Investigation and Evaluation) working group of the European Commission representative (Stefan James)
- Academic Research Consortium (Patrick Serruys - Chairman)

- European Heart Journal/EuroIntervention representatives (William Wijns - Associate Editor EHJ, Patrick Serruys – Editor-in-Chief EIJ)
- Institute of Social and Preventive Medicine and Clinical Trials Unit, University of Bern (Peter Jüni, Director)
- CVPath non-profit organization, Gaithersburg, USA (Michael Joner)
- CardioMed Device Consultants, consultant to CVPath, former FDA reviewer (Semih Oktay)

Decision making within this Task Force was based on unanimity for explicit recommendations. The experts of the writing and reviewing panels completed declarations of interest forms on what might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). The Task Force received its entire financial support from the ESC and EAPCI without any involvement from the healthcare industry. Notwithstanding, the ESC-EAPCI Task Force acknowledges an intrinsic conflict of interest as a direct result of the professional activities of its members as practitioners, researchers and advisors. The final report of this Task Force was submitted for external review to the ESC Task Force on Medical Devices chaired by Profs. Panos Vardas and Alan Fraser.

Clinical Context

Epidemiology and Pathophysiology of Coronary Artery Disease

Coronary artery disease remains the leading cause of mortality in Europe. Patients with angina have a substantially higher mortality risk than the average population, with coronary standardized mortality ratios around 2.5–5.2 at age 45–65 years, and approximately 1.2–2.0 at age 75–89 years.

Coronary atherosclerosis is a chronic inflammatory disease characterized by lipid retention and fibroatheromatous lesion formation. Vulnerable plaques underlying acute coronary syndromes (ACS) are in the majority of cases non-flow obstructing but have features such as a large necrotic core and thin fibrous cap predisposing to plaque rupture or erosion. Obstructive

coronary artery lesions progressively reduce the ability to increase blood flow in response to changing metabolic demands and lead to myocardial ischaemia at rest or during exercise.

Treatment of coronary artery disease aims to relieve symptoms and ischaemia, and prevent premature cardiovascular death and progression of disease. Depending on its symptomatic, functional, and anatomical complexity, coronary artery disease can be treated by medical therapy alone or combined with revascularization. Revascularization by either percutaneous coronary intervention or coronary artery bypass grafting is performed as treatment of flow-limiting coronary stenoses to reduce myocardial ischaemia and its manifestations. Moreover, PCI in the setting of ACS represents a treatment to stabilize culprit lesions and prevent abrupt or recurrent vessel closure, thereby reducing the risk of recurrent myocardial infarction and improving prognosis. The evidence for revascularization in the treatment of stable coronary artery disease and ACS is extensively reviewed in the recently published ESC guidelines on myocardial revascularization.

Medical Therapy

Medical therapy and other secondary prevention strategies to achieve risk factor modification and permanent improvements in lifestyle are cornerstones in the treatment of ischemic heart disease. Medical therapy after PCI to reduce the risk of adverse cardiovascular events includes statin therapy, antithrombotic therapy, treatment with ACE-inhibitors in selected patients, antihypertensive agents in patients with arterial hypertension, and antidiabetic therapy with appropriate treatment goals in diabetic patients. Patients also require counselling to adopt a healthy lifestyle (including smoking cessation, regular physical activity, and a healthy diet) and encourage adherence to their medication plan.

Percutaneous Coronary Intervention

PCI has become one of the most commonly performed medical procedures worldwide and recent projections predict on-going increase in procedural numbers (**Figure 1**). Minimal-invasive revascularization of coronary arteries by angioplasty was pioneered by Grüntzig in 1977. Balloon

angioplasty was limited by the risks of abrupt vessel closure due to dissections as well as restenosis and prompted the development of intracoronary devices to maintain lumen integrity, namely coronary artery stents. The first two coronary stents were implanted independently in 1986 by Puel and Sigwart in a patient with abrupt closure and another patient with restenosis, respectively. In conjunction with improvements of antithrombotic therapy, coronary stents improved procedural safety and efficacy to an extent, which extinguished the need for standby coronary artery bypass grafting, and established stenting as standard of care. However, stent mediated arterial injury elicited a neointimal hyperplasia leading to restenosis and need for ischemia-driven repeat revascularization in up to one third of patients.

Drug-eluting stents (DES) with controlled release of antiproliferative agents at the site of injury were introduced in the late Nineties to address this limitation. Stents eluting sirolimus and paclitaxel were the first DES to receive CE mark in 2002 and 2003 respectively. Numerous randomized trials consistently observed improved clinical outcomes with both DES compared with bare metal stents (BMS), primarily due to a substantial reduction in the risk of repeat revascularization. However, at the ESC Congress in 2006 a number of reports questioned the long-term safety of DES, resulting in a reduction in their use, intense scrutiny by regulatory agencies, and recommendations to extend dual antiplatelet therapy for ≥12 months. Review of the available evidence at that time revealed that early generation DES compared with BMS were associated with similar risks of death and myocardial infarction but an increased, albeit small, risk of stent thrombosis beyond one year after stent implantation, highlighting the importance of long-term follow-up (5 years after implantation).

The introduction of new generation DES with thinner stent struts, novel durable or biodegradable polymer coatings, and antiproliferative agents, has improved upon the safety profile of early generation DES by significantly reducing the risk of stent thrombosis during long-term to a level comparable with BMS. Of note, the improved safety profile did not compromise DES efficacy which was instead further improved with a significant reduction in the risk of repeat revascularisation and constitutes the current standard of care in all patient and lesion subsets with favourable long-term results. Notwithstanding, stent technology continues to

evolve and novel DES have been developed or are currently under clinical investigation (**Figure 2**). All of these technologies aim to further improve arterial healing, avoiding long-term complications, and potentially reducing dual antiplatelet therapy duration.

Bioresorbable stents provide support to the vessel wall for a defined period after PCI and are resorbed subsequently. Bioresorbable stents may offer potential advantages over the permanent metallic stents.[1] Their superior conformability and flexibility compared to conventional stents reduce altered distribution of the tissue biomechanics and preserves vessel geometry.[2] The liberation of vessel from a metallic cage can help in restoration of physiological vasomotion, mechanotransduction, adaptive shear stress, late luminal gain (as opposed to late luminal loss with permanent stents), and late expansive remodelling.[3]

Devices of Interest

Coronary stents are classified as high-risk devices by regulatory authorities in Europe and the United States (Class III medical devices). The current document focuses on the following medical devices (with or without ancillary medicinal substances) related to the field of percutaneous coronary intervention:

- BMS
- DES with and without bioresorbable coatings
- bioresorbable stents with and without drug-elution

There was no intention in this document to deal with special indication coronary stents (stent grafts or dedicated bifurcation stents), drug-coated balloons or adjunctive technology for PCI such as rotablation, thrombus aspiration, and atherectomy.

CHAPTER 2: EXISTING LEGISLATION

The evaluation for EU market approval of coronary stents falls under the Medical Device Directive[4], that was adopted in 1993. Several amendments are in place. The directive covers all Medical Devices, apart from Active Implantable Medical Devices and In Vitro Diagnostic Medical Devices, for which separate directives are in place. This main legal framework is complemented by non-binding guidance.

Legal document: Council directive 93/42/EEC1993

The Council directive 93/42/EEC1993 is the result of EU harmonization of laws governing the safety and performance of medical devices. It has been amended by the 2007/47/EC directive[5] and compliance with the revised directive became mandatory in March 2010. In order for a manufacturer to legally place a medical device on the European market, the requirements of the directive have to be met.

Devices are assigned to four groups according to risk (I/IIa/IIb/III). Stents are in class III and therefore require 'explicit prior authorization with regard to conformity'.

Devices considered to meet the essential requirements, other than devices which are custom-made or intended for clinical investigations, must bear the CE marking of conformity when they are placed on the market. A 'conformity assessment procedure' involving one or more Notified Bodies is required, in which safety and conformity with legal requirements must be documented. The requirements are broadly defined in the directive's Annex I. The devices must be 'designed and manufactured in a way that when used under the conditions and purposes intended, they will not compromise the clinical condition or the safety of the patient, or the safety or health of the users'. The device must 'achieve the performance intended by the manufacturer'.

It also broadly defines the clinical data required to document clinical safety and performance. This can be based on published or unpublished data on market experience of the device or a similar device for which equivalence can be demonstrated, a prospective clinical investigation,

or results from a clinical investigation or other studies reported in the scientific literature of a similar device for which equivalence can be demonstrated.

Specific requirements for the assessment of coronary stents are laid out in advisory documents.

Advisory documents

EMEA/CHMP/EWP/110540/2007[6]

The EMEA/CHMP/EWP/110540/2007 document is a guideline on the 'clinical and non-clinical evaluation during the consultation procedure on medicinal substances contained in drug eluting coronary stents'. It contains advice on required in vitro and animal data regarding pharmacodynamics, pharmacokinetics and toxicology. The clinical part of the document guides the clinical pharmacokinetic testing, clinical surrogate measures and exploratory testing and outlines appropriate confirmatory clinical trials.

MEDDEV 2.7.1 Annex 1[7]

Issued by the European commission in 2008, this MEDDEV 2.7.1 Annex 1 aims to guide manufacturers and Notified Bodies on the clinical evaluation of coronary stents. It defines preclinical tests according to ISO standards and provides advice on appropriate clinical trial design, including suggestions for performance assessment, clinical, surrogate and safety endpoints.

It also specifies requirements for a literature review prior to CE marking, which must be performed by a suitable qualified person and 'should include explanations dealing with both negative as well as positive publications'.

Competent authority

Competent authorities are national authorities which are responsible for the authorisation of many of the medicines available in Europe that are not authorised by the European Commission on the recommendation of the European Medicines Agency. Most competent authorities have a

Medical Device Unit. Depending on the location of the medical device manufacturer or its representative, the first placing on the market of a medical device must be notified with the corresponding competent authority.
(http://ec.europa.eu/health/medical-devices/links/contact_points_en.html)

Notified bodies

Notified Bodies are the only recognised third party bodies that can carry out a conformity assessment laid down in the relevant harmonised European standards or European Technical Assessment. The range of possible notifiable tasks includes: product certification; factory production control (FPC) certification; and determination of the product-type on the basis of type testing.

Notified Bodies are designated by Member States of the European Economic Area (EEA) as well as by other countries (e.g. Switzerland or Turkey) having signed a specific agreement with the EU. A list of all officially designated Notified Bodies under the Construction Products Regulation (CPR) is available in the database NANDO-CPR. Notified bodies must be independent of the stent manufacturers as defined in the Council Directive.

Obtaining CE mark

In order to obtain the CE conformity marking for coronary stents the manufacturer has to employ a Notified Body of his choosing. The Notified Body will review the technical dossier, assess manufacturer's quality management system and evaluate the submitted non-clinical and clinical evidence. The Notified Body will define the required literature research, non-clinical and clinical data for the CE marking of coronary stents. The Notified Body is guided by the legal and advisory documents described above (EMEA/CHMP/EWP/110540/2007, MEDDEV 2.7.1 Annex 1) but can be flexible in the interpretation.[8]

The main objective of the CE mark is to document that a device is safe and that it achieves the performance intended by the manufacturer. The process is illustrated in **Figure 3**. Once CE mark

is granted, the device can be sold on the EU market. The CE mark does not guarantee approval of funding by healthcare providers in the individual EU member states.

Post market evaluation

The importance of post market evaluation has been outlined in the Council Directive and specified for stents in the MEDDEV 2.7.1.[7] Whilst non-binding, it is strongly suggested that 'an appropriate post-market clinical follow-up program in accordance with MEDDEV 2.12/2 shall be performed for all DES and innovative stents and for all BMS unless duly justified'. This can be in the form of a clinical investigation and/or a registry. Either should include a clearly stated objective, a scientifically sound design and a study plan that justifies the patient population. Current recommendation is for a minimum duration of 3 years (MEDDEV 2.7.1) for all stents and 5 years (EMEA/CHMP/ EWP/110540 /2007) for DES.

Investigational device research

Premarket approval research studies are governed by the Council Directive and outlined in Annex VIII. The manufacturer or his authorized representative established in the EU must notify the competent authorities of the Member States in which the investigations are to be conducted. The manufacturer may commence the relevant clinical investigation at the end of a period of 60 days after notification, unless the competent authorities have notified him within that period of a decision to the contrary based on considerations of public health or public policy. Member States may authorize manufacturers to commence the clinical investigations before the expiry of the period of 60 days, in so far as the relevant ethics committee has issued a favourable opinion.

Comparison with other regulatory systems

The process of evaluation for market approval of coronary stents differs in the major regulatory systems.[9] In the United States this is the responsibility of the U.S. Food and Drug Administration (FDA). Coronary stents are in the highest risk class III and approval follows the regulatory pathway of premarket approval application (PMA). Evaluation focuses on reasonable assurance of safety and efficacy, with the requirement for a new device to provide clinically significant

benefits. In order to conduct clinical trials in the United States, FDA approval of an Investigational Device Exemption (IDE) must be obtained. Clinical data supporting the PMA for coronary stents result from the 'pivotal' trial, which may or may not be preceeded by initial feasibility studies. The process is illustrated in **Figure 3**.

The FDA commonly asks for clinical follow-up for stent trials of 3-5 years. Post-approval clinical studies that collect and report real-world outcomes are often required as a condition of PMA approvals. Approval of a device by the FDA does not lead to automatic reimbursement by the payers. The EU legislation emphasizes safety and performance for the intended use; post-marketing surveillance is strongly recommended.

The process of market approval of coronary stents is often significantly quicker in the EU, resulting in earlier availability of novel stent products to the healthcare systems. As a result, the market strategy of stent manufacturers often involves introduction of stents outside the US (OUS) first. Recent FDA initiatives aim to expedite PMA process, balancing the burden of data requirements between pre and post market evaluation.[10] New pathways are being established for early feasibility studies.[11] A summary comparison of market approval in EU and in the US is provided in **Table 2**.

The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan is responsible for market approval. Pre-market approval (Shonin) from the Ministry of Health, Labour and Welfare (MHLW) Minister is required and will be granted based on the scientific review at PMDA. Japan does not accept CE marking and/or an FDA certificate although European and US approval does help to expedite the review process.

CHAPTER 3: OBSTACLES TO APPROVAL IN EUROPE

Obstacles related to approval process

The current approval process for medical devices and clinical trials in Europe is fragmented and requires improvement. The obstacles for approval of coronary stents can be classified within two major categories:

1) obstacles related to the complexity of the approval process per se;

2) obstacles related to obtaining evidence on safety and efficacy of devices through clinical trials.

A key issue is that in Europe the processes of device approval and clinical trial conduct are regulated by two collaborating agencies, namely Notified Bodies and Competent Authorities; in the United States on the other hand, both processes are regulated by a single agency, the FDA (**Figure 3**).

A central component of the current medical device approval process is the interaction between Notified Bodies and Competent Authorities. While issuing of CE marking is controlled by Notified Bodies, the regulation of clinical trials is performed by Competent Authorities (see **Chapter 2**). In interpreting EU directives on medical devices Notified Bodies refer to MEDDEV. 2.7.1 Rev.3 for guidance. However this document just sets principals and is non-binding; Notified Bodies have to rely on communication with Competent Authorities for details.

As an example, as part of the process of obtaining a CE mark for a coronary stent from a Notified Body, a manufacturer is often required to undertake a clinical trial. Indeed manufacturers often consult with Notified Bodies on the design of clinical trials. However, it is a legal requirement that the manufacturer notifies and receives approval for the trial from the relevant Competent Authority (so called Clinical trial Notification). Such a dual consultation process is not ideal as Competent Authorities and Notified Bodies may differ in terms of interpretation of some aspects of the EU directives.

A further level of complexity is added by the fact that in Europe each Member State has its own Competent Authority and a variable number of Notified Bodies (ranging from none to numerous). Moreover, there are some Notified Bodies located in non-EU countries. All of these Notified Bodies have varying application procedures and requirements. For example in terms of Clinical Trial Notifications the Medical Device Directive indicates that the Competent Authority has 60 days to review the notification. However this is not universally adhered to by all countries and different countries have various "clock" stopping rules that cause unpredictable delays. Moreover requirements for trial submission vary among Competent Authorities: for example some Competent Authorities require Ethics Committee approvals prior to submitting the Clinical Trial Notification, some allow parallel submission. Thus it can easily be appreciated that harmonization of the process for device and clinical trial approval might be advantageous.

Proposed changes to the approval process

The EU Commission proposed in September 2012 a number of measures to improve both the designation and monitoring of Notified Bodies[12], including the creation of a Member State authority body, the Medical Device Coordinating Group (MDCG) to work together with the Commission to improve oversight of Notified Bodies. Key activities of MDCG oversight are:

1) to review applications of entities proposing to become Notified Bodies ("Initial Qualification", Art. 32);

2) to perform periodic auditing of existing Notified Bodies ("On-going Monitoring"(Art. 35);

3) to select random products under Notified Body review, which will be subjected to an additional "scrutiny" procedure by the MDCG (Art. 44).

The policy objective of this scrutiny procedure intended to increase patient safety by ensuring that Notified Bodies are adhering to professional standards and that clinical evidence presented by manufacturers is reviewed and approved by independent clinical experts. However, the proposed regulatory framework may introduce additional uncertainty regarding the expected timelines for approval of medical devices in Europe, and this should be avoided.

The Task Force understands the critical importance of high performance quality of Notified Bodies. Measures to improve the quality of Notified Bodies performance are strongly

welcomed: reduction in their number across Europe, identification and designation of Notified Bodies with special expertise in particular areas of investigation, harmonization of the approval process between various Notified Bodies, and introduction of more stringent processes for auditing of Notified Bodies. However, the Task Force has considerable concerns regarding the proposed "scrutiny" mechanism, which involves the random selection of products under review by Notified Bodies for additional auditing. A random check on selected dossiers would introduce variable and unpredictable delays and may considerably lengthen the time taken for device approval without tangible benefit for patient safety. Moreover, focusing efforts on individual dossiers may not be as effective as introducing additional measures targeted at Notified Bodies approval processes. In this respect, the Task Force would instead propose changing legislation to compelling Notified Bodies to publish details of and rationale for the decisions on individual dossiers. This would ensure maintenance of high quality processes and act as a form of "auto-scrutiny". Moreover it seems sensible to consider the implementation of a standard timelines for the overall approval process (e.g. 3-6 months from submission to approval), which should be enforced by competent authorities at the national level.

In summary the general objective of new regulations for coronary stent approval should be based on transparent rules and a simplified process, without "extra layers" of oversight. In addition the EAPCI Task Force recommends that the approval process should be complemented by clearer mandates for rigorous post-marketing surveillance.

Obstacles related to clinical trial regulation

Gathering clinical evidence regarding safety and efficacy of coronary stents constitutes an important part of the approval process for coronary stents and other devices discussed in this document. However, the current scenario in Europe poses numerous obstacles for launching clinical trials: cost, administrative burdens and legal constraints in the conduct of clinical research, all of which constitute major roadblocks without evident benefit for patient care. Regulations on clinical trials are complex, often confusing and vary considerably according to country introducing inequalities and inhomogeneity in trial conduct across European member states. In this respect the Task Force supports harmonization and streamlining initiatives such as

Voluntary Harmonization Procedure.[13] Moreover many of these requirements are superfluous and add nothing to the main objectives of the individual trial, with the additional risk of deflecting attention away from the most pertinent safety aspects of the clinical investigation. Importantly, the resulting spiralling costs act as an important disincentive to launching adequate clinical trials and to obtaining high quality medical evidence.[14]

Recently, a number of obstacles in the conduct of randomized clinical trials were highlighted by members of the Sensible Guidelines Group.[15] Thus, the initiation process to conduct a clinical trial requiring approval from multiple different entities including all competent authorities of participating EU countries and ethics committee approval from all participating institutions not only impose delays but may require changes in trial conduct to accommodate regional interpretations of EU directives. Other obstacles identified by the Sensible Guidelines Group include the disproportionate focus on retrospective source data verification instead of applying less costly centralized statistical monitoring procedures; and the overemphasis of suspected adverse event reporting of indivual cases instead of the more effective review of safety data by independent data and safety monitoring committees.

Proposed changes by the European Commission to clinical trial regulation

The European Commission has addressed issues in relation to clinical trial regulation with a proposal to re-engineer the European Union Clinical Trials Directive. Some of the modifications foreseen in this revision include allowing co-sponsorship, developing a single EU portal to submit applications, designation of a single reporting member state coordinating the response of all the member states involved, introduction of pre-specified, strict timetables for submissions, review and decisions on trials, and definition of situations in which informed consent may be waived (e.g. in trials performed in emergency situations). Some scientific organisations and researchers have called for a more radical change to the regulatory environment for clinical trials[16, 17] while others have challenged the viability of some of the proposals in the current of non-uniform regulation across the different European countries.[18]

CHAPTER 4: RISK ANALYSIS

Definition

ISO 14971 defines risk as the "combination of the probability of occurrence of harm and the severity of that harm." Risk management for medical devices is "the systematic application of management policies, procedures and practices, to the tasks of analyzing, evaluating, monitoring and controlling risk." Definitions related to risk management are summarized in **Table 3**.

Therefore, the general principle underlying risk management to the field of coronary stents is to:

- Identify potential hazards related to coronary stents
- Evaluate potential hazards taking into account the generally accepted state of the art
- Eliminate or reduce hazards related to coronary stents to an acceptable level
- Continuously update and document hazards during the entire product life cycle

Coronary stent systems are composed of several components such as metallic or bioresorbable stent platform, the delivery system, and coatings. Therefore, the risks associated with each device component and the system as a whole should be considered in the risk analysis.

Risk Analysis

Risk analysis of a coronary stent system is based on its intended use and identification of characteristics related to its safety, followed by the identification of hazards and estimation of the associated risks.

Risk Evaluation

Risk evaluation refers to the process of comparing estimated risks against given risk criteria to determine acceptability of individual risks. In this regard, given risk criteria may be derived from risks evident from coronary stents already in clinical use or from the evaluation of clinical study data especially for novel technology (bioresorbable stents) or new intended uses. It is important to consider all available data and state of the art information such as technology and practice update existing at the time of design.

Risk Control

Risk control refers to the process in which decisions are made and measures implemented by which risks are reduced to or maintained within specific limits. This specific process includes an analysis of risk associated with the introduction of risk control measures. In addition, residual risk evaluation must be performed resulting in a risk/benefit analysis.

Specific Risks Associated with Coronary Stent Systems

There are common clinical risks associated with intravascular stents and stent systems. Specific design features of each product type, whether they are BMS, DES or bioresorbable stents will require a thorough risk analysis that should address risks specific to each device design. Risk analysis should be performed considering ISO 14971: 2012 and ISO 13485. Risk analysis should be a continuous process throughout the life cycle of the product. The most commonly known risks associated with clinical consequences are listed in **Table 4**.

Risk mitigation associated with coronary stents is identified in non-clinical and clinical assessment sections of this document (**chapter 6**). An overview of selected historical examples of coronary stents that failed in clinical practice are summarized in **Table 5**.

CHAPTER 5: SYSTEMATIC REVIEW OF CE-MARKED CORONARY STENTS

As integral part to inform this report, a systematic review was performed to summarize available evidence of randomized clinical trials on CE-marked coronary artery stents and bioresorbable stents. The pre-specified timeframe for evidence to be included in the systematic review ranged from 1 January 2002 to 20 October 2013. The systematic review was performed under the lead of the Institute of Social and Preventive Medicine, University of Bern, Switzerland.

Aim

The systematic review had several objectives:

1) To establish a contemporaneous summary report of the safety and efficacy of coronary stents studied during the last decade.
2) To assess the safety and efficacy across various stent generations ranging from BMS over early generation DES to new generation DES.
3) To systematically evaluate angiographic follow-up data across various stent generations ranging from BMS over early generation DES to new generation DES.
4) To provide detailed information about individual CE marked coronary artery stents previously not available to the public.
5) To provide the basis for objective performance criteria (OPCs) in the field of coronary artery stents.

Methods

Identification of CE-Marked Coronary Stents And Bioresorbable Stents

In the absence of a publicly available list of CE-marked coronary devices, the Task Force obtained data from CvPipeline – a private database of cardiovascular markets owned by MarketMonitors Inc. – on commercially available CE-marked coronary stents. The list was updated for completeness in June 2014 (see **Table 1)**.

Search Strategy and Abstract Screening

On 14 October 2013, Task Force searched several electronic databases, without language restrictions, including the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE through Ovid and PubMed. We restricted the searches to publication year 2002 to 2013. A detailed overview of the applied combinations of search terms is provided in the **Appendix A**. In addition, Task Force contacted content experts and screened reference lists of recent systematic reviews on the topic.

Data Extraction

Four investigators independently extracted data, with disagreement resolved in consultation with another investigator. Outcome data were extracted at the time of the primary endpoint and the time of latest follow-up for each trial. Various trial characteristics were assessed including the quality of trial monitoring and adjudication, the features of included patient and lesion populations, and the collection of pre-specified primary and secondary endpoints (clinical and angiographic). A dedicated database was used for data extraction.

Pre-specified Clinical and Angiographic Outcomes

Pre-specified clinical outcomes were all-cause death, cardiac death, myocardial infarction, target-lesion revascularization, and definite stent thrombosis.

Pre-specified angiographic outcomes were in-stent minimal lumen diameter, in-stent late lumen loss, in-segment binary restenosis, in-segment percent diameter stenosis.

Statistical Analysis

Trial characteristics and clinical and angiographic outcomes were evaluated overall and by stent groups, distinguishing between BMS and DES. DES were further classified according to device generation (ie, early vs. new) and according to approval by the FDA. In addition, outcomes for specific DES types were summarized.

The Cypher sirolimus-eluting stent, the Taxus paclitaxel-eluting stent (Taxus and Taxus Element) and the Endeavor zotarolimus-eluting stent were considered “early generation” DES for the

purpose of this study. “New generation” DES refer to a class of all subsequent DES with published evidence of at least 1000 patients included into randomized clinical trials. Based on this definition, the following stents were considered new generation DES: the Xience, Promus and Promus Element everolimus-eluting stents, the Resolute zotarolimus-eluting stent, the BioMatrix and Nobori biolimus-eluting stents, and the Yukon Choice PC and Yukon Choice PF sirolimus-eluting stents. New generation stents with FDA approval were Xience, Promus and Promus Element everolimus-eluting stents, the Resolute zotarolimus-eluting stent at the time of the review. Bioresorbable coronary stents were not included in the review due to absence of published randomized clinical evidence to date.

Main population characteristics evaluated were mean age of the patients (in years) and prevalence of female patients, diabetic patients, stable coronary artery disease, unstable angina, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction, multivessel disease, left main disease, bifurcation lesions, bypass lesions, in-stent restenosis lesions and chronic total occlusion. Trials performed exclusively in patients aged 75 years or older were categorised as trials performed in elderly patients. Any trial performed in a dedicated subgroup, such as diabetic patients, or patients with ST-elevation myocardial infarction were classified as such.

Summary data were reported as rates per 100 person years, counts with percentages, medians with interquartile range and means with standard deviation. Summary data were reported overall, per category and per main population characteristic.

Results

As summarized in **Figure 4**, Task Force retrieved 5609 citations in total, 5584 from the bibliographic searches, in which Task Force retained 151 unique trials, and 25 from expert contact and screening of reference lists, in which Task Force identified 7 trials missed by the bibliographic searches

Patient and Trial Characteristics

A total of 158 randomized clinical trials were identified. Summary characteristics of the identified trials are provided in **Supplementary Table 1,** whereas characteristics of the

investigated populations are summarized in **Supplementary Table 2**. A subgroup of trials investigated the use of coronary stents in specific patient and lesion subsets, as presented in **Supplementary Table 3**. Patient characteristics according to stent group are reported in **Supplementary Table 4**.

Overall Clinical and Angiographic Outcomes

Overall clinical outcomes at the time of the primary endpoint assessment (median 12 months, interquartile range [IQR] 9-12 months) are reported in **Supplementary Table 5**. Overall angiographic outcomes at the time of angiographic surveillance (median 8 months, interquartile range 6-9 months) are reported in **Supplementary Table 6**.

Clinical and Angiographic Outcomes According to Stent Group

Overall clinical and angiographic outcomes according to stent group are reported in **Supplementary Table 7 and 8**, respectively. Stent groups included: any DES, any BMS, early generation DES, new generation DES, and FDA approved new DES.

Clinical outcomes according to stent group in trials assessing the primary endpoint at 9-12 months are reported in **Tables 6 and 7**, respectively.

Among patients treated with BMS, rates of all-cause death, myocardial infarction, target-lesion revascularization, and definite stent thrombosis were 2.29% (IQR 1.64-3.79%), 3.29% (IQR 1.97-4.31%), 12.32% (IQR 7.44-13.79%), and 1.08% (IQR 0.57-1.94%), respectively.

Among patients treated with DES, rates of all-cause death, myocardial infarction, target-lesion revascularization, and definite stent thrombosis were 1.67% (IQR 0.99-2.59%), 2.88% (IQR 1.41-4.57%), 4.00% (IQR 2.05-6.40%), and 0.61% (IQR 0.37-0.99%), respectively.

Among patients treated with early generation DES, rates of all-cause death, myocardial infarction, target-lesion revascularization, and definite stent thrombosis were 1.64% (IQR 0.94-

2.76%), 2.88% (IQR 1.39-4.59%), 4.34% (IQR 2.40-7.11%), and 0.74% (IQR 0.45-1.19%), respectively.

Among patients treated with new generation DES, rates of all-cause death, myocardial infarction, target-lesion revascularization, and definite stent thrombosis were 1.92% (IQR 1.05-2.54%), 2.89% (IQR 1.45-4.21%), 2.91% (IQR 1.67-5.94%), and 0.47% (IQR 0.28-0.72%), respectively.

Figure 5 summarizes median event rates with IQR for all-cause death, myocardial infarction, target-lesion revascularization, and definite stent thrombosis in patients treated with BMS, early generation DES, and new generation DES. **Figure 6** provides summary data of the median cumulative frequency of in-stent late lumen loss with IQR in patients treated with BMS, early generation DES, and new generation DES.

Clinical and Angiographic Outcomes in Specific Subgroups

Clinical and angiographic outcomes in specific patient and lesion subgroups are reported in **Supplementary Tables 9 to 18.** Specific patient populations included: all-comer patient populations, patients with ST-segment elevation myocardial infarction, diabetes and elderly patients (>75 years of age). Specific lesion populations included: presence of multivessel, left main, or saphenous vein graft disease, in-stent restenosis, bifurcation lesions and chronic total occlusions.

Supplementary Tables 9 and 10 summarize outcomes for patients treated with any DES. **Supplementary Tables 11 and 12** report outcomes for patients treated with BMS. **Supplementary Tables 13 and 14** show outcomes for patients treated with early generation DES. **Supplementary Tables 15 and 16** tabulate outcomes for patients treated with new generation DES. Finally, **Supplementary Tables 17 and 18** tabulate outcomes for patients treated with FDA approved new generation DES.

Clinical and Angiographic Outcomes According To Specific DES Types

Clinical outcomes for all individual DES types are reported in **Supplementary Table 19**. Angiographic outcomes for all individual DES types are reported in **Supplementary Table 20**.

CHAPTER 6: EVALUATION PLAN FOR CORONARY STENTS

CHAPTER 6A: INTENDED USE AND CLAIMS

The vast majority of PCI procedures performed currently involve balloon angioplasty and stent deployment. This section provides guidance on the intended use of stents and claim of outcomes with stents.

Intended use of coronary stents

The basic mechanisms underlying coronary stenting are relief of obstruction (lumen enlargement) and maintenance of patency thereby ameliorating myocardial ischaemia. The clinical objectives of coronary stenting are two-fold:

1. Symptom relief - alleviating angina pectoris for patients who are symptomatic despite medical therapy.[19] Data supporting the use of coronary stents for this indication have been summarized in the recent ESC Guidelines on myocardial revascularization and are tabulated in **Table 8**.
2. Prognostic benefit - preventing cardiac death, recurrent myocardial infarction and heart failure in patients with high ischemic burden[20, 21] or acute coronary syndromes.[22] Data supporting the use of coronary stents for this indication have been recently published and are summarized in **Figure 7**.[23]

It is prudent that the clinical protocol of a coronary stent clearly describes the intended use of the device. FDA recommends that the sponsor should identify, as clearly and precisely as possible, the intended use of the stents, including the specific indications about the lesion types (e.g. de novo, in-stent restenosis), lesion dimensions, anatomical application (native coronaries, left main, bifurcation etc.) and target population (e.g. stable angina, acute coronary syndrome etc.).[24]

Claims for outcomes

Claim is a statement of treatment benefit. The claims can be primary, secondary and exploratory. A claim can appear in any section of a medical product's FDA-approved labelling or in advertising and promotional labelling of devices. The intended use should be linked with the outcome claims. FDA guidance suggests that the clinical protocol for a coronary stents should include the criterion for study success (claim). The objectives of the clinical trial should be to demonstrate the efficacy (patient benefit) and safety (morbidity and mortality) of the device for a defined claim in a target population under specific conditions of intended use. Based on intended use, the claims can be prognostic, symptomatic or both (**Figure 8**).

Clinical (including death, cardiac death, myocardial infarction, stroke and revascularization) or imaging outcomes (e.g. angiographic late lumen loss, minimal lumen diameter, percent diameter stenosis etc. or intravascular ultrasound parameters) are commonly used valid endpoints for making outcome claims.[25] These endpoints are discussed in detail elsewhere.[26] However, there is also growing emphasis on patient reported outcomes.

Patient reported outcomes (PRO)

Patient reported outcomes (PRO) is a measure of health status that comes directly from the patient without amendment or interpretation of the response by a clinician or anyone else. A PRO can be measured by self-reporting or during an interview provided that the interviewer records only the patient's response. The outcome can be measured in absolute terms (e.g., severity of a symptom, sign, or state of a disease) or as a change from a previous measure.

FDA has produced a detailed guidance on use of PRO to make a claim and obtain product labelling.[27] Generally, findings measured by a well-defined and reliable PRO instrument in appropriately designed investigations can be used to support a claim in medical product labelling if the claim is consistent with the instrument's documented measurement capability.[27] However, there are certain challenges and requirements to accomplish PRO based labelling.

- PRO are useful when device is used for symptomatic benefit but not applicable when it is used to achieve prognostic benefit (for example, patients with acute myocardial infarction

or prognostically significant silent ischaemia).

- If PRO is to be used as trial outcome, blinding and randomization are important to avoid bias and placebo effect. Patient blinding is possible in device vs device studies but not PCI against medical or surgical treatment. In such situations, sponsors can use techniques that may minimise the effects of possible unblinding.[27] Open-label trials or trials with suspicion of inadvertent unblinding are unlikely to get approval for labelling claims based on PRO instruments. However, if a PRO instrument appears useful in assessing patient benefit in such situations, sponsors should consult relevant authorities to discuss it upfront.
- It remains debatable whether to use PRO only as secondary endpoint or whether PRO can be used as primary endpoint of a trial if the link with pathophysiological or clinical endpoints has been established. However, for time being, we suggest using PRO as supportive or secondary endpoints.
- The recall period i.e. time patients are asked to consider in response to a PRO item or question can be momentary (real time) or retrospective of varying lengths. It is important to consider patients' ability to reliably recall the information requested. In many cases, what is of real interest is not the integrated effect over a short time period (e.g., 2-week period), but the effect at regular intervals (e.g., 2, 4, and 6 weeks).[27] There are some specific recommended recall times for some instruments, for example, 4 weeks for Seattle Anginal questionnaire.
- A PRO instrument (e.g. a questionnaire) to measure treatment benefit or risk should have proven capability to measure the concept claimed. It is ideal to have baseline (before randomisation) and follow-up evaluation in all study arms to compare both absolute and relative change in measured outcomes.
- Trial should have adequate power to detect change in PRO endpoints. Statistical plans especially how to handle multiple endpoints and missing data should be explicitly described.

Bioresorbable stents

The intended use of bioresorbable stents devices is the same as permanent metallic stents but claims may differ particularly as it relates to long-term benefits. Therefore, the process of development and approval should be similar. However, these devices may need additional

assessment to document bioresorption. Considering that bioresorbable stent may have better conformability, return of vasomotion and potential late lumen enlargement, they may reduce recurrence of chest pain or angina and improve exercise tolerance and quality of life as compared with metallic DES. Therefore, additional PRO endpoints for bioresorbable stents remain an attractive choice as secondary endpoints. However, further data are needed before PRO can be accepted as primary endpoint for these bioresorbable stents.

CHAPTER 6B: NON-CLINICAL ASSESSMENT

The purpose of this Section is to provide a risk based non-clinical assessment plan for coronary stents, including BMS, DES with permanent or biodegradable components, and completely bioresorbable stents. Non-clinical assessment includes laboratory, bench or in vitro testing, as well as pre-clinical evaluation in animal models. An important objective of European regulatory legislative for medical devices should be to warrant uniformity and transparency of non-clinical investigation and, most importantly, to ensure device safety. In this respect non-clinical studies represent a very important measure of successful practical implementation of these key objectives prior to clearance to clinical investigation. In this chapter, the Task Force provides guidance for non-clinical assessment of coronary stents and for the evaluation of fully bioresorbable stents. A checklist for non-clinical studies performed according to GLP standards is provided in **Table 9**.

1.0 References

The following documents are primarily developed based on well-known risks and to identify non-clinical and clinical test requirements in order to mitigate the risks related to the BMS and DES indicated for coronary arteries:

1. MEDDEV 2.7.1 – Appendix 1: Evaluation of Clinical Data for Manufacturers and Notified Bodies, Appendix 1 – Clinical Evaluation of Coronary Stents (December 2008)
2. ANSI/AAMI/ISO 25539-2:2012: Cardiovascular implants -- Endovascular devices -- Part 2: Vascular stents
3. Guidance for Industry and FDA Staff - Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (April 2010)
4. Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems - Draft Guidance for Industry and Food and Drug Administration Staff (Aug 2013)
5. FDA Coronary Drug-Eluting Stents—Nonclinical and Clinical Studies (March 2008)
6. FDA Coronary Drug-Eluting Stents: Companion Document—Nonclinical and Clinical Studies (March 2008)

7. EMEA/CHMP/EWP/110540/2007: Guideline on the clinical and non-clinical evaluation during the consultation procedure on medicinal substances contained in drug-eluting (medicinal substance-eluting) coronary stents
8. Health Canada Pre-Market Guidance on Bare Cardiovascular Stents (2004)
9. FDA Guidance on Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications (2013)
10. Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters
11. ISO 10555: Intravascular catheters -- Sterile and single-use catheters – Parts 1 through 5
12. ISO 10993 Biological Evaluation of Medical Devices (this is for biocompatibility)
13. ASTM Standard F2129 Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices
14. ASTM Standard G71 Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes
15. ASTM Standard F2182 Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging (This is MRI safety related test)
16. ASTM Standard F2503 Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment (This is MRI safety related test)
17. FDA Guidance for Industry and FDA Staff: General Considerations for Animal Studies for Cardiovascular Devices (2010)

2.0 Risk Analysis

Although, the common clinical risks associated with intravascular stents are well understood, specific design features of each product type, whether they are BMS, DES or bioresorbable stents, will require a thorough risk analysis that should address risks specific to each device design. The following sections provide recommendations for the non-clinical assessment of coronary stents and to mitigate risks associated with each product type (i.e., BMS, DES (with non-degradable and degradable coatings) and completely bioresorbable stents).

3.0 Bare Metal Stents

Non-clinical tests to mitigate risks associated with BMS include bench, biocompatibility and in-vivo studies. The requirements for these tests are well described within the MEDDEV 2.7.1, Appendix 1 document and also in the FDA Guidance Documents for BMS and DES. This section details existing recommendations for non-clinical testing of BMS with an update based on recently identified clinical adverse events related to longitudinal stent deformations.

3.1 Bench Testing

In general, the bench testing should be performed in three categories that will cover safety issues associated with the stent materials, the stent design and the delivery system. Bench testing should be performed covering full range of device sizes and designs, and the sample size per each device size should be justified. Bench testing should be performed on finished devices unless justified. The ESC Task Force recommends that the bench testing should assess all of the characteristics as listed below. Note that all of these tests are aligned with the FDA BMS Guidance Document.

3.1.1 Material Characterization

3.1.2 Stent Dimensional and Functional Attributes

- **3.1.2.1** Dimensional Verification
- **3.1.2.2** Percent Surface Area
- **3.1.2.3** Foreshortening
- **3.1.2.4** Stent Longitudinal Strength
- **3.1.2.5** Recoil for Balloon Expandable Stents
- **3.1.2.6** Stent Integrity
- **3.1.2.7** Radial Stiffness and Radial Strength
- **3.1.2.8** Radial Outward Force (if self-expanding)
- **3.1.2.9** Mechanical Properties
- **3.1.2.10** Stress /Strain Analysis
- **3.1.2.11** Fatigue Analysis

3.1.2.12 Accelerated Durability Testing

3.1.2.13 Particulate Evaluation and coating durability (If coated)

3.1.2.14 Magnetic Resonance Imaging (MRI) Safety and Compatibility

3.1.2.15 Radiopacity (stent visibility)

3.1.2.16 Additional Tests for Stents Intended for In-Stent Restenosis

3.1.2.17 Additional Tests for Stents Intended for Bifurcation Lesions

3.1.2.18 Corrosion Potential of Coronary Stents

3.1.3 Delivery System Dimensional and Functional Attributes

3.1.3.1 Dimensional Verification

3.1.3.2 Delivery, Deployment, and Retraction

3.1.3.3 Balloon Rated Burst Pressure (Balloon Expandable Stents Only)

3.1.3.4 Balloon Fatigue (Repeat Balloon Inflations; Balloon Expandable Stents Only)

3.1.3.5 Balloon Compliance (Stent Diameter vs. Balloon Pressure; Balloon Expandable Stents Only)

3.1.3.6 Balloon Inflation and Deflation Time (Balloon Expandable Stents Only)

3.1.3.7 Catheter Bond Strength

3.1.3.8 Tip Pull Test

3.1.3.9 Flexibility and Kink Test

3.1.3.10 Torque Strength

3.1.3.11 Coating Integrity

3.1.3.12 Stent Securement for Unsheathed Stents

3.2 Biocompatibility Testing

As recommended within the MEDDEV 2.7.1, Appendix 1 document and also in the FDA Guidance Documents for BMS and DES, the biocompatibility testing should be performed per the ISO standard “Use of International Standard ISO-10993, “Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.”

4.0 Metallic Drug Eluting Stents

Non-clinical tests to mitigate risks associated with non-resorbable DES include bench, biocompatibility and in-vivo studies as well as the assessment of the medicinal substance. The requirements for these tests are well described within the MEDDEV 2.7.1, Appendix 1 document and also in the FDA Guidance Documents for DES. This section details recommendations for the non-clinical testing of the DES with permanent or bio-resorbable polymeric coatings as a carrier to the medicinal or biologic substances.

4.1 Bench Testing

The non-resorbable DES is comprised of a metallic stent platform, the permanent or bioresorbable coating (drug/carrier), and the delivery system. For the metallic stent platform component, the bench testing should be performed in three categories as described above in Section 3.1. Additional or repeat testing maybe required if the surface of the stent struts are modified in order to apply the coating layer. The safety of the coating components, i.e., the medicinal or biologic substances and the polymeric carrier testing should be assessed and all associated risks should be considered when planning bench testing for non-resorbable DES. Bench testing should be performed covering full range of device sizes and designs, and the sample size per each device size should be justified. Bench testing should be performed on finished devices unless justified.

4.1.1 Metallic Stent Platform and the Delivery System Components

Please see Section 3.1 above. Note that these tests should be performed on finished DES as appropriate to eliminate the risk of potential influence of the medicinal substance and the carrier on the BMS stent performance.

4.1.2 Coating Component

4.1.2.1 Medicinal Substance

MEDDEV 2.7.1, Appendix 1 document refers Notified Bodies to a member state designated competent authority for medicinal products or to the European Medicines Agency (EMA) for their scientific opinion. The non-clinical evaluation of the medicinal substance on DES should include the following data:

4.1.2.1.1.1 Non-clinical Pharmacology and Toxicology

4.1.2.1.1.2 Clinical Pharmacology (Evaluation of the pharmacokinetics (PK))

4.1.2.1.1.3 Drug Release Kinetics

4.1.2.1.1.4 Chemistry Manufacturing Controls (CMC) for the Medicinal Substance

4.1.2.1.1.5 CMC for the Finished Product (includes the coating)

4.1.2.2 Carrier

The medicinal substance carriers on DES are generally polymeric in nature. Most carriers are made from permanent polymers while some DES are available with biodegradable carriers. The clinical risks associated with both types of carriers are well described in MEDDEV 2.7.1, Appendix 1 document as well as FDA Guidance Documents. The recommended bench test requirements for the carriers are described below:

4.1.2.2.1 Coating Characterization (i.e., chemistry, thickness and uniformity, adhesion to stent substrate)

4.1.2.2.2 Coating Integrity (acute and chronic)

4.1.2.2.3 Particulate Assessment

4.1.2.2.4 Stability

4.1.2.2.5 Characterization of degradation profile (if carrier is biodegradable)

4.2 Biocompatibility Testing:

As recommended within the MEDDEV 2.7.1, Appendix 1 document and also in the FDA Guidance Documents for DES, the biocompatibility testing should be performed per the ISO standard "Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." For bio-resorbable carriers, there may be a need to alter some of the standard tests such as the extraction conditions and exposure times, and separate biocompatibility testing may be needed on degradation products.

5.0 Bioresorbable Stents

Currently, there are no established standards, FDA Guidance Document or MEDDEV documents addressing non-clinical test requirements for bioresorbable stents. However, the risks associated with such products are somewhat identified based on both pre-clinical and clinical experiences from the currently marketed products, and products that are under investigational use. This section provides recommendations for the non-clinical testing of bioresorbable stents.

5.1 Bench Testing

5.1.1 Full characterization of the finished product

5.1.1.1 Molecular weight (MW)

5.1.1.2 The molecular weight distribution (PDI)

5.1.1.3 Percent crystallinity (χ_c, if applicable)

5.1.1.4 Melting temperature (T_m, if applicable)

5.1.1.5 Glass transition temperature (T_g)

5.1.1.6 Residual monomer content

5.1.1.7 Residual free radicals (if applicable)

5.1.1.8 Structural integrity

5.1.1.9 Mass loss

5.1.1.10 Degradation products

5.1.2 Mechanical testing plan should follow the list provided in Section 3.1 above. However, physiologically relevant environment should be considered when performing these tests to capture the effect of degradation on mechanical integrity over time. The results of characterization (See 5.1.1) may impact all aspects of product evaluation such as type of testing and timing of assessments. For example, acceleration of mechanical loading should be synchronized with accelerated degradation for accelerated durability testing. The duration of the accelerated fatigue testing should be determined through time of complete tissue coverage as determined by in vivo or in vitro degradation studies. Particulates testing should be performed through time of significant mass loss of the polymer.

5.2 Biocompatibility

The biocompatibility testing should be performed per the ISO standard "Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." However, there may be a need to alter some of the standard tests such as the extraction conditions and exposure times. It is also recommended that separate biocompatibility testing performed on degradation products. The following standards should be considered for the biocompatibility evaluation of the bioresorbable stents:

- ISO/TS 12417:2011
- ISO/DIS 12417-1
- ISO/TR 37137:2014
- ISO/TS 17137:2014

Also, FDA Draft Guidance Document entitled "Use of International Standard ISO-10993" provides further clarification and updated information on the use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing", April 2013. This Draft FDA Guidance incorporates information on the in vivo polymerizing and bioabsorbable materials.

5.3 In Vivo Testing

5.3.1 Animal models

To date, the preferable animal model for the assessment of coronary stents has been the *domestic crossbred or miniature swine model* or the *rabbit iliac artery model* because the size, access, and injury response appear to be similar to human vessels and may therefore be suitable for preclinical safety assessment prior to human use [28]. However, in some situations the sheep model may also be used. Comparative studies are encouraged to appropriately reflect safety and biological responses. Standard contemporary anti-platelet therapy should be utilized in all animal models. As a general rule, preclinical testing should be performed within the intended vascular territory, although there may be instances in which a switch to a different

vascular location may provide valuable information about the biological behaviour of stents owing to the differential reaction to vascular injury among species and vascular territories.

5.3.1.1 The Porcine/Rabbit Models

The normolipidemic porcine coronary artery model is the most frequently used and widely accepted animal model to study the outcome of coronary stents [28]. Miniature swine should be considered when long-term studies are performed owing to animal growth over time. Stents should be appropriately sized for the target vessel as the targeted device – to – artery ratio should be between 1.0 to 1.2 and should be implanted in naive coronary vessels. In the case of bioresorbable stents, a balloon – to – artery ratio will need to be applied, which inherently creates difficulty to appropriately size the bioresorbable stent owing to indiscernable stent struts. In addition to the assessment of safety aspects, a general appreciation of efficacy should be reflected in preclinical study design. This can be best achieved by including approved comparators with known clinical efficacy.

The advantage of the rabbit iliac artery model is the lower variability in injury and inflammation after stent implantation and therefore holds value for the study of biocompatibility and safety of investigational devices. Especially for studies focused on re-endothelialization of devices, the rabbit model may provide important advantages over swine with regards to the time course of re-endothelialization, which is slower compared to swine [29, 30]

5.3.2 Planning and conducting of preclinical studies in animals

Generally, preclinical animal studies including histopathological assessment should be performed in designated preclinical animal facilities with Good Laboratory Practice (GLP) certification. Each artery should only receive one test device except when overlapping or repeated treatment is intended. One or more arteries may be treated in a single animal depending on the specific study design. In general, study design must include appropriate controls to appreciate treatment effects especially with regards to safety and biocompatibility. When polymer-coated stents are investigated, appropriate controls consisting of either the full-component device or polymer-only coated devices should be included. Special consideration with respect to choosing appropriate control is warranted when it comes to testing of

bioresorbable stents. In our view, the ideal control should consist of a currently accepted standard of care in the specific indication in which the test product will be used clinically. A minimum of 6-8 samples per treatment group should be included in standard histopathology safety studies as well pharmacokinetic and degradation studies of bioresorbable stents. For metallic stents, a standard 28 days follow-up should be combined with a later time point of follow up of at least 90 days to capture all safety-relevant biological responses. For bioresorbable stents, critical time points of follow-up will depend on the pace of biodegradation.

5.3.2.1 Standards for Evaluation

1. Necropsy Evaluation

Thorough necropsy evaluation is key to a successful assessment of device safety and biological response. All premature and unexpected deaths need to undergo complete necropsy, gross examination of organs, tissue and histopathologic examination.

2. Tissue Processing and Fixation

Ideally, pressure-fixation at about 100mmHg with rapid exsanguination should be performed. Following fixation, organs and vessels should be sectioned transaxially at a minimum of 5mm intervals resulting in a minimum of 3 sections per stented segment (proximal, middle, distal) depending on the total length of the organ/vessel.

3. Histopathology

*Histomorphometr*y

Standard measurements have been described previously [28] and should include medial area, area within the external and internal elastic lamina, lumen area and stent area. Neointimal area and percent area stenosis can be calculated from the above mentioned areas. In addition, neointimal thickness should be measured above and between stent struts. With respect to the assessment of bioresorbable stents it is important to emphasize luminal dimensions during degradation.

Special care is needed for the assessment of bioresorbable stents. Acute and chronic inflammation should be judged on the basis of acute and chronic inflammatory cells, which mostly consist of neutrophils/monocytes acutely and lymphocytes/macrophages chronically for clearing of biodegradation products. In a similar vein, standard injury scores may be misleading at longer-term follow-up as destruction of the internal elastic lamina may result from inflammation rather than reflecting vascular residues of acute injury at the time point of stent implantation. Furthermore, special effort should be made to characterize the change in tissue composition during biodegradation by histopathology focussing on both extent and nature of neointimal tissue especially at the remnant sites of stent struts. Correlation with intravascular imaging data may be helpful to foster understanding in changes of tissue composition.

4. Clinical Observations and Blood Work

Monitoring of general health, body temperature and body weight are important measures. Blood parameters referring to the overall assessment of organ function are of particular importance prior to initiation of the study and at regular intervals thereafter.

5. Overlapping Stents and Long Stents

The safety aspect of such studies may be two-fold. Firstly, mechanical issues (fatigue) of overlapping stents must be addressed and excess injury and inflammation investigated. Secondly, synergistic effects of stent coatings (i.e. carrier matrix and/or drug) in overlapping stents need to be carefully investigated to exclude potential adverse reactions arising from local accumulation and release into the surrounding tissue. For the assessment of bioresorbable stents, overlapping stent studies are strongly recommended owing to the clinical safety aspect of overlapping bioresorbable stents struts (fracture, particulate embolization, thrombus formation, delayed healing i.e. endothelialisation etc.)

6. Intravascular Imaging

Recently intravascular imaging modalities such as intravascular ultrasound and optical coherence tomography have emerged as useful tools in the assessment of coronary stents [31, 32]

[33] [34, 35]. They allow for the evaluation of important in vivo healing parameters such as stent strut coverage, neointima formation, malapposition and thrombus formation. However, it needs to be considered that intravascular imaging may cause substantial tissue damage (i.e. endothelial loss or injury) resulting in inappropriate histopathological assessment of stents. Intravascular imaging is strongly recommended in a subset of animals in studies of bioresorbable stents as stent degradation and physiological vessel dimensions can be evaluated over time[36].

7. Statistical Comparison

Continuous parameters should be expressed as mean±standard deviation when data are normal distributed and as median with percentiles in the event of skewed data distribution. Choice of statistical test will depend on the structure and design of experiments.

8. Time Point of Follow up

In general, follow-up should capture all relevant biological processes pertaining to stent safety. If drug elution is complete by 90 days, follow-up should include a 180 days time point. If biodegradation of stents or stent components takes 1 year, time points beyond the 1-year frame are necessary to capture device safety. The addition of a late time point after bioresorption is complete is needed to document patency of the vessel, extent of neointima, absence of structural remodeling and absence of inflammation. End of bioresorption is defined as the total resolution of visible stent material or the absence of any visible changes of substitution material within the tissue at two consecutive follow-up time points. For time points later than one year the use of an approved control group is not required but may help to explain unexpected results.

9. In vitro and in vivo pharmacokinetics and Dose Finding

Release of drug from coronary stents should be examined in vitro and in vivo. In vitro investigation should serve the purpose of establishing the order of release kinetic and determination of complete release. For the examination of in vivo release kinetics, several methods of determination may be applied. Drug release can be examined by direct chemical determination or by use of radioactively labelled agents. First pass metabolism should be

evaluated by examination of drug elimination in urine. Furthermore, the order of drug release kinetic should be determined to warrant evaluation of release half-life. As there may be substantial variability in drug concentration measurements depending on the methodology applied for drug determination, a minimum of 6 different samples from each device at a minimum of 5 time points is recommended. The last time point should provide evidence that drug concentrations dropped below the level of detection. In addition to the determination of drug tissue concentration, concentration in blood, myocardium and major organs is obligatory. Drug concentration should also be measured in downstream myocardium supplied by the target artery.

The clinically proposed dose should be justified by preclinical examinations. Therefore, preclinical dose ranging is strongly recommended, establishing biological effects from sub-therapeutic to toxic levels.

10. Biochemical analysis of degradation products

In general, degradation products need to be clearly defined with respect to the physicochemical structure and their in vivo biological behaviour. With regards to the evaluation of polymeric components, gel permeation chromatography is a suitable analytical method to assess molecular weight and polydispersity index (PDI), which provide important insights into the degradation process of the stent and help explain observed biological behaviour. In this regard, it is important to correlate results from bioengineering tests with results from in vitro and in vivo degradation analysis to facilitate understanding of scaffolding function. For the assessment of metallic bioresorbable devices, other technologies may be applied to appropriately examine degradation products such as chemical analysis, micro CT analysis, scanning electron microscopy with element analysis etc.

11. Special considerations for the assessment of multi-component devices

Special attention is needed when it comes to safety assessment of multi-component devices employing bioresorbable stent backbones with either permanent or biodegradable coatings of different origin compared to the stent backbone. In these instances it is strongly recommended to investigate all stent components separately and also as full-component device. The

interaction of degradation processes among the different stent components needs to be defined as closely as possible.

CHAPTER 6C: CLINICAL IMAGING AND FUNCTIONAL ASSESSMENT

Overview of clinical evaluation

Comprehensive evaluation of coronary stent devices ideally follows on from the advanced stages of device development and bench testing and a dedicated program of non-clinical testing. These antecedent investigations prior to clinical use are typically primarily focused on device integrity and in vivo safety issues. Subsequent clinical evaluation is based on a combination of first human use evaluation, assessment of imaging and functional parameters; and assessment of clinical outcomes after intervention in a larger-scale trial.

Initial human trials typically incorporate an invasive imaging protocol aimed at supporting the claim of efficacy and safety. The most frequently used modality is coronary angiography. More recently, high resolution intracoronary imaging with the use of optical coherence tomography (OCT) and intravascular ultrasound (IVUS) has also been used to assess the arterial healing pattern particularly since the advent of DES with active release of antiproliferative substances. Subsequently a further medium-sized trial is often undertaken powered for the detection of differences in surrogate endpoints in comparison with existing control devices. This is usually based on a surveillance coronary angiography protocol and requires a study sample size of 200-500 patients.

Angiographic evaluation

The goal of coronary stent implantation is the maximization and stabilization of acute lumen enlargement during intervention, and the minimization of loss of achieved lumen gain during long-term follow-up. The previous MEDDEV advisory document defined device success as post-procedural angiographic residual stenosis <50%. Based on a review of the available literature, the Task Force recommends to revise the definition of device success, lowering the threshold to <30% as assessed by quantitative coronary angiography. Maximization of acute gain is determined predominantly by stent backbone structure and radial strength; loss of acute lumen gain, commonly referred to as late loss, is driven mainly by accumulation of tissue (so-called

neointimal hyperplasia) inside the stent in the months following intervention. The balance between these 2 processes determines to a large extent the clinical efficacy of the device. Completely bioresorbable stents results in similar acute performance. Upon bioresorption, however, these devices result in vessel remodelling, which may result in late lumen and vessel changes.

Owing to its simplicity, reproducibility and robust endpoints, angiographic surveillance remains the imaging modality of choice for the evaluation of the clinical performance of coronary stents. This is usually carried out at a protocol-specified time point after intervention, typically between 4-13 months, although delayed late loss may occur beyond this time. The advent of bioresorbable stents has also modified the angiographic follow-up schedule depending on the biodegradation duration.

Systematic analysis of both procedural and follow-up coronary angiographic films is the cornerstone of evaluation. Due to the limitations of visual estimation and online quantitative measurements, offline quantitative coronary analysis (QCA) in a centralized core laboratory with blinded outcome assessors in case of comparative studies is mandatory. Standardized image acquisition and the use of validated automated edge-detection software are important to improve reproducibility of measurements. Extensive experience with angiographic endpoints in clinical trials has been accumulated since the development of validated QCA algorithms in the 1980s.[37]

The principal angiographic endpoints of interest are listed in **Table 10**. The most well-studied are in-stent late lumen loss (defined as the difference between minimal lumen diameter [MLD] immediately post-stent implantation and MLD at follow-up), percentage diameter stenosis at follow-up angiography and in-segment binary restenosis (re-narrowing ≥ 50% within the body and margins of the stent) at follow-up angiography. These endpoints in particular have been well validated as robust surrogate markers of clinical device efficacy.[38-40] Their use permits comprehensive analysis of device performance with benchmarking against a wealth of previously published data (see **Table 7** and **Figure 6** in **chapter 5**). This issue has increasing

importance in the DES era: the antirestenotic efficacy of DES is high and as a result, large numbers of patients need to be enrolled if a study is to be powered for differences in clinical events. Use of surrogate endpoints allows the performance of comparative efficacy studies in relatively modest patient numbers, which is an important factor facilitating the on-going refinement of DES technology.

Time point of assessment

Vascular healing and neointimal hyperplasia formation after stent implantation are time-dependent processes. Accordingly the time-point of assessment is an important consideration as this may impact on comparative efficacy between competing devices. After plain balloon angioplasty stenosis increases between 1 month and 3 months after intervention and thereafter reaches a plateau. After BMS implantation serial angiographic surveillance studies have shown that neointimal hyperplasia tends to have peaked by 6 months. Following DES implantation however late loss seems to be an on-going dynamic process at least out to 2-5 years.[41, 42]

Angiographic surveillance and incidence of repeat revascularization

An important consideration is that the use of angiographic surveillance is itself associated with an increase in the absolute rate of clinical restenosis. This is because systematic surveillance often detects patients with restenosis who are below the threshold that prompts them to seek medical attention. Thus protocol mandated angiography inflates rates of repeat revascularization above those seen in real-world clinical practice. In comparative efficacy testing this may amplify *absolute differences* between comparator devices, although the *relative magnitude* of an observed treatment effect may be expected to be real.[43]

Evaluation by intravascular imaging

Although coronary angiography is the clinical standard for the assessment of coronary stents, intracoronary imaging can provide useful supplementary information. Of available modalities intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are the most commonly used. The main advantage of intravascular imaging is not only the higher resolution compared with angiography, but also that it permits direct visualization and measurement of

neointimal hyperplasia inside implanted stents, and appreciation of the arterial wall. By contrast angiographic measures of restenosis depend on luminal contour detection to derive surrogate measurements of in-stent neointimal formation and cannot visualize the arterial wall. However it should be acknowledged that due to the more sophisticated nature of the imaging protocols patients with more severe disease may be systematically excluded at both baseline and follow-up.

Intravascular ultrasound assessment

By virtue of more accurate determination of neointima magnitude, IVUS may confer superior ability to discriminate between the performances of comparator stents and can therefore reduce sample size. The principal IVUS endpoints of interest are outlined in **Table 10.**[44] Percentage intimal hyperplasia (%IH) volume quantifies the amount of neointima formed over the entire length of the stent and is a commonly used measure of stent performance. However as the introduction of DES saw a shift in restenosis morphology to a predominantly focal pattern, *maximum* %IH rather than %IH volume has been suggested as a more appropriate measure in DES trials.[45] As regards predictors of restenosis at the time of stent implantation the single major IVUS predictor is minimal cross-sectional area (MSA) at the end of the index procedure. In general however routine IVUS-guided stent implantation has not demonstrated convincing results in improving antirestenotic efficacy in the setting of randomised controlled trials.[46, 47] In addition IVUS can also quantify changes in arterial structure and atheroma burden.[48] This may be of particular importance in the long-term serial assessment of bioresorbable stents to assess vessel remodelling and changes on plaque volume. An important limitation of IVUS is that although it can directly visualise neointimal tissue within the stented segment, limited axial resolution (~150µm) precludes determination of neointimal coverage of individual stent struts at follow-up. This issue is resolved by optical coherence tomography. Use of IVUS can facilitate the detection of stent failure modes like stent fracture and recoil.[49]

Optical coherence tomography assessment

The adoption of optical coherence tomography (OCT) into the arena of coronary intervention shows considerable promise. However, experiences with the OCT-imaging for evaluation of

stent performance are still somewhat limited. Similar to IVUS, OCT allows accurate ascertainment of information relating to morphometric stent performance (see **Table 10)**.[50] However a key application of OCT technology is the assessment of vascular healing after stenting. The high resolution of OCT (approximately ten times greater than IVUS) makes *in vivo* determination of strut coverage and apposition feasible and OCT surveillance seem likely to become an important component of future DES clinical trials, perhaps ultimately as a proven surrogate of device safety.[50] In addition its high resolution facilitates detailed characterisation of neointimal hyperplasia as well as processes such as neoatherosclerosis at a tissue level.[30] However thus far histopathological correlation data remains scant and the clinical implications of OCT acquired datasets are unclear. Of note, OCT plays an important role to assess the process of biodegradation of completely biodegradable stents. In addition, it is able to determine the thickness of neointima as well as changes related to plaque morphology.

Assessment by coronary computed tomography angiography

Rapid advances in CT coronary angiography technology have significantly enhanced the diagnostic accuracy of this imaging modality: This has enabled greater spatial and temporal resolution and coupled with algorithms to reduce radiation exposure this has seen a rapid uptake of this technology for coronary artery imaging.[51] Nevertheless, its use in the assessment of stent performance remains limited at present. In addition to universal features predisposing to poor CT image quality, blooming artefacts generated by metal stent struts pose a particular problem for the assessment of in-stent luminal calibre and the quantitative adjudication of restenosis.[52] CT angiography has also been used in the assessment of bioresorbable stents as it allows serial measurements of lumen and vessel dimensions.[53]

Functional assessment

Assessment by fractional flow reserve (FFR)

The use of intracoronary devices to measure pressure proximal and distal to coronary stenosis has been an important component of the evaluation of stenosis severity since the introduction of PCI. More recently technological development has permitted incorporation of pressure sensors into standard calibre coronary guidewires and well-validated assessment algorithms

permit the reproducible evaluation of coronary fractional flow reserve (FFR).[54] The use of FFR in clinical practice can identify stenosis and restenosis that can be safely managed with conservative therapy versus those where the risk:benefit ratio favours intervention.[55, 56] However data to support FFR for the evaluation of coronary stents during follow-up does not exist and due to the high efficacy of current devices systematic FFR evaluation is unlikely to permit clinically meaningful discrimination of stent performance. In addition reports on the use of instantaneous wave-free ratio (iFR) – a novel parameter of stenosis severity that can be measured without inducing maximal hyperemia – remain preliminary in nature.[57]

Assessment of vasomotor function

Following implantation of metallic stents vasomotor reactivity of the stented segment is permanently abolished. However various algorithms exist for the assessment of vasomotor function proximal and distal to the stented segment (rapid atrial pacing, exercise testing, drug administration). Interestingly early generation DES were shown to have a negative impact on vasomotor function after stenting though iterative development seems to have addressed this issue with newer generation devices.[58] Bioresorbable stents have the potential to enable return of physiological vasomotor reactivity also in the stented segment and endpoints based on this assessment have been incorporated into clinical trials.

A summary of the use of invasive and non-invasive imaging modalities for the evaluation of coronary anatomy and function is provided in **Table 11**.

CHAPTER 6D: CLINICAL ASSESSMENT OF CORONARY STENTS

General considerations

Specifically designed clinical trials play a central role in evaluation of the safety and efficacy of new coronary stents. Such studies are undertaken following a careful assessment of the nonclinical trial data and are only indicated where the potential benefits and information to be gained risks are clear and the risks to patients are deemed to be justifiable. The data acquired is compared either implicitly or explicitly against data acquired with existing devices.

Initial first human use trials with new coronary devices have tended to be modestly-sized single-arm studies, typically enrolling a limited number of selected patients (n = 25-150). The main focus is identification of unforeseen safety issues and the assessment of general efficacy. Direct comparative efficacy testing is usually not undertaken. Subsequently a further medium-sized trial is often undertaken powered for the detection of differences in surrogate endpoints in comparison with existing control devices. The most common modality used is surveillance coronary angiography and this requires a study sample size of 200-500 patients. Following on from this an assessment of general efficacy and safety is performed in a large-scale trial, most commonly with comparative efficacy testing against a benchmark device in a trial powered for a device- or patient-specific outcome (usually requiring a sample of 1500-2500 patients).

Clinical trials of coronary stents may be designed as single-arm studies or randomized controlled trials (RCTs). Single arm studies may be used in early clinical evaluation to assess the general safety and efficacy of a novel device in isolation: these investigations are sometimes broadly termed feasibility or first human use studies. Alternatively they may be prospectively designed for comparison against historical data from a control device or against pre-defined benchmarks – so called objective performance criteria (OPC) – compiled from analysis of aggregate historical data with single or multiple devices, or state of the art medical therapy in the absence of accepted device-based treatment. RCTs are designed to compare the study stent or stents against one or more control stents with random treatment allocation and contemporaneous

treatment of subjects across the study groups. Randomized treatment allocation with appropriate allocation concealment minimizes the effect of physician treatment selection bias; both measured and unmeasured confounding factors tend to be equally distributed across the treatment arms. Outcome assessment by assessors blinded to treatment allocation and avoidance of attrition bias further increase the quality of randomized clinical trials.

Randomized trials versus trials with objective performance criteria

In general RCTs have been considered the investigation of choice for comparative efficacy research. Indeed recommendations for practitioners and guideline-writing authorities recognize the special value of RCTs by designating such studies as the highest level of evidence in assessing the efficacy of various therapeutic strategies. However, RCTs are expensive to conduct, labour-intensive, and time-consuming. Moreover generalizability of results is sometimes unclear: even in trials with broad inclusion criteria only a minority of eligible patients are actually included; moreover closer patient follow-up often results in treatment compliance rates which are higher than those seen in routine practice. In addition, in areas of medicine with rapid iterative development, such as coronary stenting, the time-lag inherent in RCT conduct often means that the devices are obsolete by the time mature trial data is available.

Single arm studies with outcome comparison against pre-defined benchmarks – so called objective performance criteria – represent an alternative to conventional RCTs. These studies provide in essence a comparison against a historical control group. Due to less complex study design, they may facilitate more rapid trial conduct, data acquisition and study reporting. Studies with OPC comparison have been used for many years for certain medical devices such as prosthetic heart valves [59] and have more recently been used in study protocols designed for the approval of coronary stents by the FDA. OPC studies may reduce clinical trial barriers, allow easier label expansions, and permit more timely evaluation of new coronary stents and conceivably earlier detection of adverse events. However the risks inherent in historical control comparison means that data endpoints must be highly standardized and that extensive datasets

must exist to guide delineation of robust performance criteria. In this respect, as a mature field coronary stenting is potentially suited to adopting this investigational approach due to the existence of standardized definitions agreed upon by academic and regulatory authorities as well as a body of clinical trial evidence (see **chapter 5**) which is larger than that acquired with any other medical devices.

Recommendations on trial design and study protocols

In consideration of the strengths and weaknesses of both RCT and studies with OPC comparison the task force recommends the incorporation of both study designs in programs for the evaluation of new coronary stents (see **chapter 8**). In addition, in view of the absence of existing published criteria on which to base OPC for new coronary stents the task force undertook a systematic review of the available literature in order to provide guidance for such criteria (see **chapter 5**).

In studies employing a randomized controlled trial there are 3 types of hypothesis testing/statistical approach that may be considered: (i) superiority, (ii) non-inferiority and (iii) equivalence. Trials with a hypothesis testing based on statistical equivalence lack clinical rationale for coronary stents and are not done (note: the use of the term equivalence in this context is not connected with term equivalence as used in relation to applications for device approval based on similarities to an existing device; see **chapter 7**). Superiority trials hypothesize advantage of the study stent over the control stent. The null hypothesis is that no difference exists between the stents; the alternative hypothesis is that a difference does exist. Typically a device-oriented composite endpoint should be preferred. This approach was frequently used when comparing BMS with DES. When comparing DES with DES however, as rates of clinical events have become very low large sample sizes are often required. Non-inferiority trials test non-inferiority of the study stent versus the control stent. The null hypothesis is that the test stent is inferior; the alternative hypothesis is that the test stent is non-inferior. The use of this design should be based on a hypothesized other advantage or benefit of the test stent in relation to the existing device; otherwise even if non-inferiority is

demonstrated a rationale is not evident for adoption of the newer device. A device-oriented composite is also usually preferred. Typically larger numbers of patients are required for noninferiority trials though this also depends on the definition in relation to an acceptable level of noninferiority.

For studies investigating novel coronary stents the key elements of trial protocols are shown in **Table 12**.

Optimized trial designs

Clinical trials can be further optimized in different ways. Clinical relevance of trial results is enhanced by crafting a good quality hypothesis, selecting the proper, state of the art comparator device for treatment in the control group. “All-comers” and pragmatic designs legitimise the generalisability of the trial results. Trial efficiency can be potentially enhanced by various techniques such as inclusion of high-risk subsets, use of adaptive regimes and weighing of composite endpoints, pragmatic design, modelling and Bayesian simulations, or incorporation of futility analysis. The combined evaluation of new devices and systemic drugs, and their interaction, usually requires large post-market surveillance studies. The SCAAR/SwedeHeart group has recently proposed to incorporate randomisation within nationwide clinical registries, which may increase clinical relevance and applicability of trial results.

Unmet Needs and Innovation

Priority should be to facilitate advances and disruptive innovations that target unmet clinical needs. There is great emphasis for the future on better biocompatibility, use of bioresorbable materials and allowance for normal physiology and regular care (imaging). With respect to coronary stents, this implies that the development and validation of bioresorbable coronary stents is of importance. Unmet needs can also be defined on clinical grounds as listed on **Table 13**, and innovative solutions intended to address these therapeutic areas in need should be encouraged.

Endpoint choice and definition

All clinical trial protocols must clearly list and define the primary and secondary endpoints of interest. For trials of coronary stents broad consensus exists from both academic and regulatory authorities on the choice and definition of endpoints.[25, 60] The availability and use of consensus definitions is a critically important feature of trials with coronary stents. In addition to facilitating standardization of approaches to data collection it reduces risk associated with comparisons between independent datasets and makes study comparison with OPC feasible.

In general, clinical endpoints relevant to the study of coronary stents should provide evidence in support of device efficacy and safety which are pathophysiologically plausible. Endpoints used in trials of coronary stents may be classified as either individual or composite. By combining individual endpoints, composite endpoints increase event rates and permit reduction in sample size. Ideally rates of individual contributing endpoints should be similar and treatment effects should be expected to be in the same direction. However composite endpoints including endpoints with treatment effects in opposing directions have also been employed to permit adjudication of net clinical benefit in certain situations.[61]

Coronary stents are used for the treatment of obstructive coronary artery disease to relief ischemia and maintain long-term vessel patency. Therefore, in coronary stent trials, endpoints which capture events clearly related to the mechanism of the study device are generally preferred. The most commonly used device oriented composite endpoint is *the composite of cardiac death, target vessel myocardial infarction and target lesion revascularization*. This is sometimes termed target lesion failure (TLF) and addresses safety and efficacy. However, with increasing duration of follow-up cardiovascular events, which may not be directly related to the study lesion, tend to predominate. For this and other reasons endpoints capturing all composite cardiovascular outcomes are also of interest. The most commonly used patient oriented composite is *the composite of all-cause death, any myocardial infarction and any revascularization*. Single component endpoints are no longer frequently used as primary

endpoint as larger numbers of patients are required to be enrolled (a notable exception was the PROTECT trial[62]).

In terms of safety endpoints, death, cardiac death, myocardial infarction and definite stent thrombosis are commonly used. All-cause death is the least biased outcome, however, it is less specific as death adjudicated as cardiac in origin in the setting of coronary stent trials. A considerable body of literature exists regarding the details of preferred definitions of myocardial infarction for use in clinical trials, discussion of which is beyond the scope of the current document.[63, 64] While there is broad agreement on the prognostic impact of spontaneous myocardial infarction (defined according to the Universal Definition of Myocardial Infarction), controversy surrounds the issue of peri-procedural myocardial infarction. The latter is particularly important when coronary stents are compared to other therapeutic options such as medical therapy or coronary artery bypass grafting. Areas of residual complexity and some degree of definition instability of the endpoint myocardial infarction relate to the adjudication of peri-procedural infarction particularly in patients with evolving ST-segment elevation and Non-ST-segment elevation myocardial infarction.[65]

Stent thrombosis is another area of increasing complexity, where the currently applied ARC definitions of early, late, very late and definite, probable and possible may not be accurate in all cases nor does it correlate with pathology or OCT imaging. Studies from the Prestige registry (www.prestige-fp7.eu) have shown that the clinical presentation of stent thrombosis has multiple causes including rupture or erosion of neo-atherosclerotic plaque, thrombosis superimposed on late restenosis, uncovered stent struts, malapposition and inflammation. Events classified as probable stent thrombosis may correspond to early death due to arrhythmia or fail to be adjudicated as definite stent thrombosis because of angiographic stent patency following thrombus resolution. Until definitions are modified, adequately adjudicating death or non-fatal myocardial infarction events as being device related requires proper analysis of all available data, including case narratives, angiography and invasive imaging or pathology, by experienced critical event committee members.

In terms of efficacy target lesion revascularization is the endpoint of choice with or without an endpoint of angiographic efficacy (see **chapter 6C**). However, target vessel revascularization may be considered as an alternative endpoint particularly in settings of difficult endpoint adjudication such as the PCI in the setting of acute myocardial infarction or the use of bioresorbable stents which disappear during a variable period of time.

The safety and efficacy endpoints recommended by the Task Force are listed in **Table 14**.

Data management, end points, and definitions

Procedures for data management must be clearly set out in the study protocol. Study events should be adjudicated and classified by an independent event adjudication committee blinded to the treatment group. Studies testing novel coronary stents are recommended to have a data safety monitoring board (DSMB) with a clearly-defined charter. Procedures for adverse event reporting should be specified with reference to requirements of local ethics committee and the competent authority.

Timing of endpoint assessment

As events may not accrue at a constant rate over time, follow-up duration and time of adjudication of the primary endpoint are important considerations. In general, events occurring within days of the intervention are considered procedure-related and follow -up should occur at 30 days (to identify possible early adverse safety issues such as stent thrombosis). Beyond this period, any endpoint related to the device is in competition with the natural course of disease. Primary endpoint assessment in coronary stent trials is typically performed at 9-12 months as this is the time period where any process related to restenosis will have reached a plateau. Thereafter yearly follow-up out to 5 years is recommended in order to detect any late adverse

event. A later time point of primary endpoint assessment at 2, 3 or 5 years may also be considered particularly in devices which address long-term rather than short-to mid-term outcomes.

Statistical analysis

A pre-specified statistical analysis plan is a central component of any clinical trial. The trial should be adequately powered to address the test hypothesis and define a standard level of alpha at which the null hypothesis should be rejected. If multiple primary endpoints are planned, issues in relation to multiple testing must be addressed either by adjustment of alpha or use of a hierarchical analysis plan. In general in trials hypothesizing superiority, an intention-to-treat analysis is preferred as it tends to be more conservative; for trials hypothesizing non-inferiority, cross-over (not treated as per protocol) may reduce differences between the study groups, so a per protocol analysis may be preferred as it is more conservative.

CHAPTER 7: DEVICE ITERATIONS

The Council Directive 93/42/EEC1993 defines equivalence as follows.

- Clinically: used for the same clinical condition or purpose; used at the same site in the body; used in similar population (including age, anatomy, physiology) ; have similar relevant critical performance according to expected clinical effect for specific intended use.
- Technically: used under similar conditions of use; have similar specifications and properties; viscosity, surface characteristics; be of similar design; use similar deployment methods (if relevant); have similar principles of operation.
- Biologically: use of same materials in contact with the same human tissues or body fluids.

This definition is also applied in MEDDEV 2.7/1 (EMEA guideline on the clinical and nonclinical evaluation during the consultation procedure on medicinal substances contained in drug-eluting coronary stents)

The Task Force proposes to differentiate between the evaluation process for new devices as opposed to device iterations.

Approval of new devices should be based on the proposed evaluation plan (see **chapter 8**). Device iterations are defined as changes of a CE-marked device of the same manufacturer without substantial modification in platform material, coating and drug, maintaining the same indication for use and similar clinical and nonclinical performance characteristics.

- Clinically: used for the same clinical condition or purpose; used at the same site in the body; used in similar population (including age, anatomy, physiology) ; have similar relevant critical performance according to expected clinical effect for specific intended use.
- Technically: used under similar conditions of use; have similar specifications and properties; viscosity, surface characteristics; be of similar design; use similar deployment methods (if relevant); have similar principles of operation.

- Biologically: use of same materials and medicinal substances in contact with the same human tissues or body fluids.

The Task Force recommends that application for device iterations should be considered on a case by case basis. In case of certain device iterations, approval may be based on nonclinical performance characteristics but not necessarily clinical performance criteria (see **chapter 8**). .

CHAPTER 8: CLINICAL DEVELOPMENT PLAN

Based on the results of the systematic review, the content discussed in the previous chapters as well as discussions with stakeholders, the task force has extensively elaborated on a potential clinical development plan to be recommended for future coronary artery stent evaluation from first-in-man investigations to post-marketing surveillance in Europe. Several key insights served as conceptual underpinning of the clinical development plan, which will be presented in this chapter.

1. The most important prerogative of this Task Force was to define the delicate balance to preserve patient safety while avoiding unnecessary delays of innovative technology before becoming available for clinical use in Europe. The dilemma between patient safety and access to novel devices for unmet clinical needs has been articulated in a discussion of the FDA on innovation.[66] The FDA has acknowledged that - due to existing barriers to innovation - initial clinical testing of novel devices has frequently been performed in non-US sites, which allowed device innovation and market approval predominantly outside of the US. Accordingly, the FDA has proposed new regulation to overcome these limitations with the aim to provide earlier and broader patient access to novel devices with clinical benefit.[67] However, this new regulatory process must be restricted to areas of limited or no alternative therapeutic choices in order to maximize patient protection. In areas with well-established therapeutic options, patient safety must be adequately ensured by appropriately designed studies.
2. The life cycle of medical devices in general and coronary artery stents in particular is short due to device iterations or innovations, which make early generation devices clinically obsolete within less than 5 years (**Figure 9**). The latter has important implications for the time from development to market approval as well as recognition of adverse events in clinical practice. The Institute of Medicine of the National Academy of Sciences (USA) has published some recommendations to be considered for device regulation.[68] Accordingly, innovative therapies that have the potential to improve public health should be facilitated by making medical devices available in a timely manner. Noteworthy, devices should be monitored throughout their entire life cycle particularly

during the post-marketing period, which may be achieved by a formal post-market surveillance. There should be an integrated regulatory framework of pre- and post-marketing aspects. This process is ideally self-sustaining and self-improving and evaluated through a continuous quality-improvement program. Although these recommendations pertain to the evaluation of the FDA 510 (k) clearance process in the evaluation of moderate risk devices, these general principles may also guide the evaluation of coronary stents in the future.

3. During its review, the task force has identified several areas of unmet need that are relevant to the field of PCI and coronary artery stents and may particularly benefit from innovative technologies. These areas of unmet are summarized in **Table 13**.

   The Task Force recognizes that - under ideal circumstances - devices should be categorized into conventional devices (treatment with well-established standard-of-care available) and innovative devices (no or limited treatment with no well-established standard-of-care available). However, this distinction may be difficult from case to case and requires careful discussion between device manufacturer, regulators and medical experts. In order to avoid any ambiguity and time-consuming discussions to resolve what is considered conventional versus innovative, the Task Force concludes that a uniform assessment remains preferable.

4. It is increasingly recognized that post-marketing surveillance importantly complements the overall clinical evaluation process. In particular, there is concern of underreporting of serious adverse events related to malfunction of medical devices following market approval. Rather than relying on self-reported adverse events, the FDA Amendments Act of 2007 demanded the FDA to implement the sentinel initiative with an integrated database-analysis model and infrastructure allowing the near real time post-marketing surveillance by scanning electronic medical records.[69, 70] Intense post-marketing surveillance of devices and drugs used in routine clinical practice may produce precious health care data, result in a learning health care system thereby enhancing patient safety. The Task Force therefore stresses the importance of long-term follow-up in populations representative of routine clinical practice and proposes the concept of conditional market approval (see **Figure 10**).

5. A recent analysis of clinical trial evidence which was used by the FDA to approve novel therapeutic agents between 2005 and 2012 showed a wide range of quality, follow-up duration and mix between clinical and surrogate endpoints.[71] Trial evidence resulting in CE-approval as it relates to coronary artery stents shows even greater heterogeneity. Therefore, this Task Force recommends a uniform process with consistent quality parameters leading to pre- and post-marketing device approval based on findings of the systematic review included in this document.
6. The results of the systematic review on coronary artery stents presented in this document revealed that contemporary coronary artery stents achieve a high and predictable clinical safety and efficacy. In addition, clinical and angiographic endpoints to evaluate the performance of coronary artery stents are well matured. Therefore, the Task Force proposes to consider objective performance criteria in the future evaluation of coronary artery stents that may serve as reference during early clinical investigations. However, adoption of this concept will require regular and formal updates of the systematic review included into this report.
7. Although there has been progress in the transparent reporting of clinical outcome data, there remains room for improvement. The US Trial and Experimental Studies Transparency (TEST) Act from 2012 importantly expands the reporting requirements of clinical trials by demanding that any clinical trial of drugs or devices regardless of phase are registered on ClinicalTrials.gov, results are reported within 2 years of study completion, protocol and consent documents approved by Institutional review boards are included in result reports, and foreign trials used to support market-approval are registered.[72] Currently there is no public access to non-clinical and clinical investigations leading to CE-approval. Similarly, the decision process of Notified Bodies leading to device approval is not publicly available. Although post-marketing data are shared among different Competent Authorities, this information is not readily disclosed. The Task Force is aware of the sensible nature of some data including intellectual property issues, which require protection. However, the Task Force proposes to consider the following processes:

a. to implement a systematic public registration process for all clinical investigations leading to CE-approval
b. to publish the decision making process of Notified Bodies leading to CE approval of medical devices on a publicly accessible website
c. to share the results of post-marketing surveillance publicly
d. to create a central publically-accessible depository for all coronary stents with CE approval and related clinical trial evidence

8. Depending on the geographic origin of clinical trial data, there is considerable variation in terms of experience in clinical trial conduct, clinical trial methodology and quality, ascertainment of adverse event and adjudication. Moreover, clinical trial data may be influenced by cultural and ethnic background (i.e. resistance to dual antiplatelet therapy). This Task Force therefore recommends to recruit a minimum of one-third to half of all patients in Europe for clinical trials with medical devices intended to support application for CE-mark approval.
9. There is considerable variability in duration from submission to definite CE-approval. The Task Force considers timely response and review of submitted files essential for a successful approval process. It recommends that the review process should be monitored and completed within a pre-specified time – ideally within 3-6 months. Along the same line, the conduct of clinical trials should be facilitated. The clinical trial submission process should include pre-defined timelines for approval of clinical trial initiation in participating European countries and call for a concerted European ethics committee review procedure.
10. The instructions for use should provide clear guidance as to the appropriate indications and contra-indications for a particular device.

In view of these considerations, the Task Force proposes the evaluation of novel coronary devices (both coronary artery stents and bioresorbable stents) according to the diagram summarized in **Figure 10**.

Satisfactory completion of the extensive non-clinical investigations as described in **chapter 6B** is the prerequisite for any pre-market approval study. The Task Force emphasizes the importance of complete and transparent reporting of all non-clinical investigations that clearly address any potential safety and efficacy concerns. Sophisticated methodology in the non-clinical evaluation of coronary devices will minimize subsequent risk of the clinical evaluation plan.

The device manufacturer will propose a clinical study based on a pre-specified claim of equivalence or potential benefit compared with OPC versus the current standard-of-care. The design for the pre-market approval study will typically consist of a study with a pre-specified OPC control assessed at 9-12 months follow-up. In case OPC for a specific intended use are lacking the Task Force recommends that a randomized controlled trial should be done.

To derive an empirical basis for optimal performance criteria (OPC) for the angiographic endpoint in-stent late lumen loss, the Task Force performed a random-effects meta-analysis separately for BMS, early and new generation DES of trial arms with available angiographic data. Pooled estimate and corresponding between-trial variance were used to fit a cumulative distribution curve by stent group that could be used as a nomogram to derive OPC for future DES evaluated in pre-approval single-arm studies. We used the nomogram to derive the 50th percentile of in-stent late lumen loss expected as mean in-stent late lumen loss in future single-arm studies and the 95th percentile of mean in-stent late lumen loss to be excluded by the one-sided 95% confidence interval and used sampsi for one-sample comparisons in Stata 12.1 to derive the number of patients required to achieve greater than 80% power to exclude the 95th percentile at a one-sided alpha of 0.05 (**Figure 11**).

A device manufacturer may prefer to conduct a randomized trial rather than use a pre-specified OPC. This approach will be possible if the comparator arm adheres to the same pre-specified criteria and endpoints as defined for the OPC. If the pre-specified outcomes are fulfilled against the pre-specified OPC, the product may receive conditional CE-mark approval.

Following conditional CE-mark approval, the device manufacturer is mandated to initiate, conduct and complete a compulsory randomized clinical trial powered for clinical endpoints within 36 months of CE-mark approval. The comparator arm in this randomized trial is defined as the current standard-of-care. This comparator arm must adhere to the same pre-specified criteria and endpoints as defined for the OPC. The trial design of superiority or non-inferiority is based on the claim of the manufacturer (equivalence or potential benefit compared with standard-of-care) with a follow-up for the primary endpoint of typically 12 months.

If the novel device fulfills the pre-specified primary endpoint outcomes, long-term follow-up of the entire cohort is mandatory throughout 5 years with completion of a final report at which time unconditional CE-approval is granted. If the novel device does not fulfil the pre-specified primary endpoint outcomes, extension of the trial and additional studies may be coordinated in discussion with the regulatory agencies prior to CE-mark withdrawal. Alternatively, CE-mark approval may be withdrawn and the device will be no longer available for clinical use.

Bioresorbable coronary stents should be directly compared with a CE-approved metallic DES or with other CE-approved bioresorbable coronary stents. The comparator arm must adhere to the same pre-specified criteria and endpoints as defined for the OPC.

9. REFERENCES

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10. TABLES

TABLE 1. LIST OF CE-APPROVED DRUG-ELUTING CORONARY STENTS AND BIORESORBABLE STENTS

Device name	Producer
Absorb	Abbott
Acrobat SES	Svelte
Active	Cordynamic
Amazonia PAX	Minvasys
Apollo	Intek
ARTAX	Aachen Resonance
AXXESS	Biosensors
BioFreedom	Biosensors
BioMatrix	Biosensors
BioMime Aura/Morph	Meril
BiOSS Expert	Balton
BiOSS LIM	Balton
CARLO S	Balton
Combo	OrbusNeich
Coracto SES	Alvimedica
Coraxel	Alvimedica
Coroflex Please	B. Braun
Coroflex ISAR	B. Braun
Cre8	CID
Cypher/Cypher select	Cordis
DESolve/DESolve 100	Elixir Medical
DESyne BD	Elixir Medical
DESyne Nx	Elixir Medical
Endeavor	Medtronic
Eucatax PES	Eucatech
Firebird	Microport
Genuis TAXCOR	Eurocor
Indolimus	Sahajanand
Infinnium	Sahajanand
Intrepide	Clearstream
Itrix	AMG
Janus	CID
Luc-Chopin2	Balton
M'Sure-S	Multimedics

Device name	Producer
MAGICAL	EuroCor
MiStent	MiCell
Neo:DrugStar ST	MeoMedical
Nevo	Cordis
Nile PAX and Delta PAX	Minvasys
NOBORI	Terumo
Omega	Globamed
OPTIMA JET	CID
ORSIRO	Biotronik
PARTNER	Lepu
PAXEL	Balton
Pico Elite PES	AMG
PROLIM	Balton
PROMUS	Boston Scientific
PROMUS Element	Boston Scientific
ProTAXX	Vascular Concepts
Release-R	Relisys
Release-T	Relisys
Resolute/Resolute Integrity	Medtronic
Self-Apposing PES	Stentys
Sparrow	Biosensors
Supralimus	Sahajanand
Supralimus-Core	Sahajanand
Synergy	Boston Scientific
TAXCOR/TAXCOR Plus	EuroCor
TAXCOR Polymer Free	EuroCor
TAXUS Express/Liberté/Element/ION	Boston Scientific
Ultimaster	Terumo
Vita Stent	Aachen Resonance
XIENCE V/PRIME/SBA/nano/Xpedition	Abbott
XLIMUS	Cardionovum
YUKON Choice PC	Translumina
YUKON Choice PF	Translumina
ZoMaxx	Abbott

TABLE 2. MARKET APPROVAL PROCEDURES IN EUROPE AND THE UNITED STATES OF AMERICA

	European Union	United States	Comment
Premarket investigations approval	National competent authorities and local ethic committees	FDA Investigational Device Exemption (IDE)	Time to approval for clinical studies tends to be faster in the EU
Market approval granting body	Notified Body (NB)	FDA	Approximately 80% of FDA funding is public and 20% derived from user fees. NB are mostly private companies
Requirements	Safety and performance as intended	Safety and effectiveness	Clinical trials for FDA approval are somewhat larger
Post market evaluation	Recommended; required for reimbursement in some countries	Required post market device study as part of PMA approval	Role of postmarket evaluation increasing in both systems
Transparency	Data not publically accessible; NB decisions and EUDAMED not accessible	Summary data published post PMA approval; MAUDE registry publically accessible	More transparency in FDA process on review, recalls and decisions
Reimbursement	National/regional commissioning with variable requirements	CMS clearance & code	Single market entry in US vs. multiple markets in EU
Geographic requirement for clinical trial data	Undefined	Requirement for 50% data in US population	-

FDA, Food and Drug Administration; NB, notified body; PMA, IDE, Investigational Device Exemption; PMA, premarket approval

TABLE 3. DEFINITIONS RELATED TO RISK MANAGEMENT

Term	Definition
Harm	Physical injury or damage to the health
Risk	Combination of the probability of occurrence of harm and the severity of that harm
Hazard	Potential source of harm
Severity	Measure of the possible consequences of a hazard
Risk Estimation	Process used to assign values to the probability of occurrence of harm and the severity of that harm
Safety	Freedom from unacceptable risk
Risk Analysis	Systematic use of available information to identify hazards and to estimate the risk
Risk evaluation	Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk.
Risk Assessment	Overall process comprising a risk analysis and a risk evaluation
Risk management	Systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk
Risk Control	Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels
Residual Risk	Risk remaining after risk control measures have been taken

TABLE 4. STENT FAILURE MODES AND CLINICAL CONSEQUENCES

Device Components	Failure Modes	Potential Clinical Risks
Stent Platform	Stent Fracture, Stent Recoil, Longitudinal Deformation, Lack of Visibility, Non-Optimal Radial Stiffness, Crimped Profile and Flexibility, Biocompatibility	Stent Thrombosis, Restenosis, Deliverability, Geographical Miss, Myocardial Infarction, Need for Additional Stenting, Inflammation
Stent Coating (Polymer)	Lack of Coating Integrity (Delamination, Webbing Cracking, Peeling, Ridging), Particulates Generation, Non-Uniformity, Biocompatibility	Stent Thrombosis, Embolism, Restenosis, Myocardial Infarction, Edge Effects, Inflammation
Medicinal Substance	Non-Uniform Dose Density (Toxicity), Biocompatibility	Delayed Healing, Stent Thrombosis, Embolism, Hypersensitivity, Prolonged anti-platelet therapy
Bioresorbable Stent Related	Radial Stiffness (acute and long-term), Stent Recoil, Visibility, Crimped Profile, Flexibility, Structural Integrity, Particulates Generation, Biocompatibility	Stent Thrombosis, Restenosis, Geographical Miss, Myocardial Infarction, Need for Additional Stenting, Inflammation
Delivery System	Flexibility, Pushability, Particulate Generation, Shaft Kinking, Stent Securement, Balloon Rupture	Procedural Success, Embolism, Vascular Injury, Thrombosis, Stent Loss, Vessel Damage

TABLE 5. SELECTED EXAMPLES OF CORONARY STENT FAILURES

Device	Rationale	Problem	Lessons learned regarding approval process	CE / FDA approval	References
Gold plated stent (NIRoyal)	Gold coating of stainless steel stents was designed to increase radiopacity and improve biocompatibility	RCT (n=603) performed after marketing of the NIRoyal gold plated stent demonstrated a higher rate of restenosis at 6 months with the the NIRoyal stent compared to stainless steel stent	Insufficient clinical assessment of safety and efficacy prior to approval	CE approval FDA approval	[73, 74]d
^{32}P radioactive stent (Isostent)	Implantation of low-dose 32P radioactive β-emitting stents hypothesized to reduce restenosis	Unanticipated delayed arterial healing and edge effects		No CE approval No FDA approval	[75]
Taxol sleeve stent (QuaDS)	Drug-delivery QuaDS stent used acrylate polymer sleeves loaded with paclitaxel derivative hypothesized to reduce restenosis	Increased rates of stent thrombosis, MI, and death	Insufficient pre-clinical assessment prior to approval inflammatory	CE approval No FDA approval	[76]
Actinomycin-eluting stent	Drug-eluting stents with doses of actinomycin D of 2.5 and 10 μg/cm2) were	Malignant proliferative restenosis identified in first-in-man study	Long-term follow-up of instrumented animals might have identified this issue	No CE approval No FDA approval	[77]

	hypothesized to suppres neointimal formation above the stent.				
NEVO stent	The NEVO used reservoir technology to facilitate drug loading and release	Problems with stent securement	Incomplete risk assessment	CE approval No FDA approval	[78]

FDA, Food and Drug Administration

TABLE 6. SYSTEMATIC REVIEW RESULTS - CLINICAL OUTCOMES IN CORONARY STENT TRIALS WITH PRIMARY ENDPOINT ASSESSMENT AT 9-12 MONTHS

	N of contributing patients/trials	Outcomes at 9-12 Months Median (25%-75% IQR) Per 100 Person Years
All-cause Death (%)		
BMS	7011/21	2.29 (1.64 to 3.79)
DES	63535/75	1.67 (0.99 to 2.59)
Early DES	31937/63	1.64 (0.94 to 2.76)
New DES	31598/37	1.92 (1.05 to 2.54)
FDA approved new DES	20835/27	1.88 (1.01 to 2.47)
Cardiac Death (%)		
BMS	5891/15	1.57 (0.88 to 2.81)
DES	59334/59	1.00 (0.53 to 1.69)
Early DES	29149/48	0.98 (0.50 to 1.83)
New DES	30185/32	1.00 (0.65 to 1.63)
FDA approved new DES	20135/25	0.99 (0.58 to 1.39)
Myocardial Infarction (%)		
BMS	6315/19	3.29 (1.97 to 4.31)
DES	62347/71	2.88 (1.41 to 4.57)
Early DES	30976/59	2.88 (1.39 to 4.59)
New DES	31371/36	2.89 (1.45 to 4.21)
FDA approved new DES	20833/27	2.78 (1.33 to 4.26)
Target Lesion Revascularisation (%)		
BMS	5557/17	12.32 (7.44 to 13.79)
DES	57595/67	4.00 (2.05 to 6.40)
Early DES	26729/56	4.34 (2.40 to 7.11)
New DES	30866/35	2.91 (1.67 to 5.94)
FDA approved new DES	20436/26	3.01 (1.75 to 4.72)
Definite Stent Thrombosis (%)		
BMS	6399/19	1.08 (0.57 to 1.94)
DES	54393/58	0.61 (0.37 to 0.99)
Early DES	24221/46	0.74 (0.45 to 1.19)
New DES	30172/31	0.47 (0.28 to 0.72)
FDA approved new DES	19634/22	0.43 (0.28 to 0.58)

BMS, bare metal stents; DES, drug-eluting stents; FDA Food and Drug Administration

TABLE 7. SYSTEMATIC REVIEW RESULTS – ANGIOGRAPHIC FOLLOW-UP OUTCOMES IN CORONARY STENT TRIALS

	N of contributing patients/trials	Median (25%-75% IQR)
In-stent Late Lumen Loss (mm)		
BMS	5659/42	0.90 (0.70 to 1.01)
DES	31903/108	0.25 (0.14 to 0.44)
Early DES	19467/94	0.30 (0.16 to 0.45)
New DES	9698/34	0.18 (0.13 to 0.25)
FDA approved new DES	5051/24	0.16 (0.13 to 0.22)
In-segment Percentual Diameter Stenosis (%)		
BMS	5403/37	40.90 (36.80 to 44.40)
DES	29713/100	24.71 (20.90 to 30.45)
Early DES	19969/88	25.37 (20.70 to 30.45)
New DES	7355/31	23.15 (21.36 to 28.15)
FDA approved new DES	4256/22	22.75 (18.80 to 24.10)

BMS, bare metal stents; DES, drug-eluting stents; FDA Food and Drug Administration

TABLE 8. REVASCULARIZATION VERSUS MEDICAL THERAPY: ANGINA, EXERCISE TIME, AND NUMBER OF MEDICATIONS AT EARLY AND LATE FOLLOW-UP

Study	Angina		Exercise Time		Number of Medications	
	Early	*Late*	*Early*	*Late*	*Early*	*Late*
ACME[79]	64% vs. 46%* free of angina at 6 months	62% vs. 47%* free of angina at 3 years	11.2 min vs. 9.5* min exercise time duration at 6 months	10.0 min vs. 8.5* min exercise time duration at 3 years	30% vs. 50% on β-blocker*, 35% vs. 71% on CCB*, and 24% vs. 50% on nitrate* at 6 months	28% vs. 39% on β-blocker, 47% vs. 72% on CCB*, and 24% vs. 52% on nitrate* at 3 years
RITA-2[80, 81]	19.4% vs. 35.9%* at 3 months	15.0% vs. 21.4%* at 5 years	37 s in favor of PCI* at 3 months	25 s in favor of PCI* at 3 years	37% vs. 57% on ≥2 drugs at 3 months	31% vs. 45% on ≥2 drugs at 5 years
AVERT[82]	Improvement in angina 54% vs. 41%* at 1.5 years	-	-	-	61% vs. 60% on β-blocker, 44% vs. 49% on CCB, and 50% vs. 60% on nitrate at 1.5 years	-
TIME[83]	Significant improvement in angina class at 6 months	No differences in angina class at 1 year	-	-	Significant reduction of number of drugs at 6 months	Significant reduction of number of drugs at 1 year
MASS II [84, 85]	21% (PCI) vs. 12% (CABG) vs. 54% (MT) free of angina* at 1 year	41% (PCI) vs. 36% (CABG) vs. 57% (MT) free of angina* at 10 years	-	-	-	-
SWISSI II[86]	-	-	Max workload at bicycle ergometry 169 W vs. 148 W* at 4 years	Max workload at bicycle ergometry 173 W vs. 136 W* at 10 years	49% vs. 86% on β-blocker*, 21% vs. 51% on CCB*, and 12% vs. 47% on nitrate* at 4 years	39% vs. 84% on β-blocker*, 17% vs. 32% on CCB, and 4% vs. 45% on nitrate* at 10 years
COURAGE[87]	56% vs. 47%* free of angina at 6 months	59% vs. 56% free of angina at 3 years	-	-	85% vs. 89% on β-blocker, 40% vs. 49% on CCB*, and 53% vs. 67% on nitrate* at 1 year	85% vs. 86% on β-blocker, 42% vs. 52% on CCB*, and 40% vs. 57% on nitrate* at 5 years

*P<0.05. CCB=calcium-channel blocker, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, MT=medical therapy, W=watts. (Adapted from the ESC Guidelines on Myocardial Revascularization 2014 Eur Heart J; in press)

TABLE 9. CHECKLIST FOR NON-CLINICAL STUDIES PERFORMED ACCORDING TO GLP STANDARDS

Test Modalities	Most Relevant Documents

Bioengineering
• Risk Analysis
• Bench Testing
• Material Characterization
• Stent Dimensional and Functional Attributes
• Delivery System Dimensional and Functional Attributes
• Coating Component Characterization
  ○ Medicinal Substance Characterization
  ○ Complete Characterization of
  ○ Biodegradation in BRS
• Biocompatibility
	• EMEA/CHMP/EWP/110540/2007: Guideline on the clinical and non-clinical evaluation during the consultation procedure on medicinal substances contained in drug-eluting (medicinal substance-eluting) coronary stents
	• MEDDEV 2.1/3 rev 3
	• Guidance for Industry and FDA Staff - Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (April 2010)
	• Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems - Draft Guidance for Industry and Food and Drug Administration Staff (Aug 2013)
	• FDA Coronary Drug-Eluting Stents—Nonclinical and Clinical Studies (March 2008)
	• FDA Coronary Drug-Eluting Stents: Companion Document—Nonclinical and Clinical Studies (March 2008)

Toxicity	• ISO 10993 Biological Evaluation of Medical Devices

Safety Studies
• In Vivo Information
  ○ Angiography
  ○ Device Deployment Procedures
  ○ Device Acute Performance
  ○ Complications
  ○ Final Angiography and Intravascular Imaging at Follow Up
  ○ Clinical Information and Blood Work
  ○ Necropsy Information
• Histopathology
  ○ Histomorphometry
  ○ Assessment of Inflammation
  ○ Assessment of Thrombus Formation
	• EMEA/CHMP/EWP/110540/2007: Guideline on the clinical and non-clinical evaluation during the consultation procedure on medicinal substances contained in drug-eluting (medicinal substance-eluting) coronary stents
	• MEDDEV 2.1/3 rev 3
	• ANSI/AAMI/ISO 25539-2:2012: Cardiovascular implants – Endovascular devices -- Part 2: Vascular stents
	• FDA Coronary Drug-Eluting Stents—Nonclinical and Clinical Studies (March 2008)
	• FDA Coronary Drug-Eluting Stents: Companion Document—Nonclinical and Clinical Studies (March 2008)
	• FDA Guidance for Industry and FDA Staff: General Considerations for Animal Studies for Cardiovascular Devices (2010)

○ Characterization of Strut Degradation in BRS ○ Characterization of Tissue Composition During Degradation in BRS • Intravascular Imaging ○ Morphometric Assessment ○ Judgement of Strut Coverage ○ Characterization of Strut Degradation in BRS ○ Assessment of Thrombus Formation	• Tearney GJ et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol. 2012;59(12):1058-72 • Prati F et al. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. Eur Heart J. 2010;31(4):401-15.
Pharmacokinetic Studies • In Vitro Pharmacokinetics • In Vivo Pharmacokinetics • Establishment of In Vitro – In Vivo Correlations	• EMEA/CHMP/EWP/110540/2007: Guideline on the clinical and non-clinical evaluation during the consultation procedure on medicinal substances contained in drug-eluting (medicinal substance-eluting) coronary stents • MEDDEV 2.1/3 rev 3 • FDA Coronary Drug-Eluting Stents—Nonclinical and • Clinical Studies (March 2008) • FDA Coronary Drug-Eluting Stents: Companion Document—Nonclinical and Clinical Studies (March 2008
Biochemical Analysis of Degradation Products in BRS • Definition of Degradation Products • In Vitro Degradation Profile • In Vivo Degradation Profile • Establishment of In Vitro – In Vivo Correlations	• Use of International Standard ISO-10993, “Biological Evaluation of Medical Devices Part 1: Evaluation and Testing • ISO/TS 12417:2011 • ISO/DIS 12417-1 • ISO/TR 37137:2014 • ISO/TS 17137:2014

BRS, bioresorbable stent

TABLE 10. IMAGING ENDPOINTS FOR CORONARY STENT EVALUATION

ANGIOGRAPHY ENDPOINTS
- Reference vessel diameter, mm - Minimal lumen diameter (in-stent, in-segment), mm - Percentage diameter stenosis (in-stent, in-segment), % - Late loss (in-stent, in-segment), mm - Binary restenosis (in-stent, in-segment), %
INTRAVASCULAR ULTRASOUND ENDPOINTS
- Stent area, mm2 - Mean lumen area, mm2 - Minimal lumen area, mm2 - EEM area, mm2 - Plaque area, mm2 - Neointima area, mm2
OCT ENDPOINTS
- Stent area, mm2 - Lumen area, mm2 - Neointimal thickness, mm - Neointimal area, mm2 - Percent volume obstruction, % - Uncovered stent struts, % - Malapposed stent struts, % - ISA distance, mm - ISA area, mm2
CT ANGIOGRAPHY ENDPOINTS
- Reference vessel area, mm2 - Mean lumen area, mm2 - Minimal lumen area, mm2 - Reference vessel diameter, mm - Minimal lumen diameter, mm - Mean percentage area stenosis, % - Mean percentage diameter stenosis , %
FUNCTIONAL ASSESSMENT ENDPOINTS
- Fractional flow reserve

- iFR
- Vasomotor function assessed by change in mean lumen diameter between pre- and post-nitrate QCA
- Vasomotor function assessed by change in minimal lumen diameter between pre- and post-nitrate QCA

TABLE 11. INVASIVE AND NON-INVASIVE EVALUATION OF CORONARY ANATOMY AND FUNCTION

Evaluation of coronary anatomy and stents

Non-Invasive

- The use of MRI and other hybrid imaging is not recommended
- Coronary angiography with Multislice CT: not recommended except for sequential follow-up of bioresorbable stents, when technically possible

Invasive

- IVUS has become obsolete except for the quantitation of expansive or constrictive remodelling
- IVUS Virtual Histology can be marginally useful when used sequentially for the evaluation of tissue/plaque response to implant
- OCT is the preferred modality and can address a number of detailed features among which strut malapposition & coverage, lumen & stent dimensions, ackward patterns, tissue prolapse and thrombus, edge analysis.

Evaluation of coronary function

Non-Invasive

- High-sensitivity troponin release indicates myocardial damage caused by the procedure (requires pre- and post-PCI measurements)
- CT FFR post-PCI has the potential to evaluate adequacy of procedural functional result but needs further validation

Invasive

- Post-PCI FFR and delta FFR from pre-PCI has the potential to evaluate adequacy of procedural functional result but needs further validation
- IMR can be used for evaluation of microvascular resistance
- Vasomotor function testing can evaluate both the vasomotor range and coronary response to various stimuli (exercise, graded acetylcholine infusion, pacing-induced tachycardia)

MRI, Magnetic Resonance Imaging; CT, computed tomography; IVUS, intravascular ultrasound; OCT, optical coherence tomography; FFR, fractional flow reserve.

TABLE 12. MINIMUM REQUIREMENTS FOR TRIAL PROTOCOLS INVESTIGATING CORONARY STENTS

Primary study hypothesis(es)
List of primary and secondary endpoints
List of inclusion and exclusion criteria
Definitions of endpoints of interest
Description of interventional procedures and devices
Details of data monitoring and event adjudication procedures
Randomization procedures/concealment allocation, stratification, blinding/masking measures (if applicable)
List of pre-specified subgroups of interest
Data analysis plan (including details of intention-to-treat or per protocol analysis)
Assumptions used for sample size calculation
Existence and composition of DSMB
Procedures for adverse event reporting
Detailed study timeline including planned remedial measures
Ancillary documents: Case report forms Patient informed consent forms
Trial registration on a publically-accessible website

TABLE 13. UNMET NEEDS AND THE FIELD OF CORONARY REVASCULARIZATION

Clinical settings
- Patients with diabetes mellitus
- Patients with end-stage chronic kidney disease
- Patients with extensive and diffuse multivessel coronary artery disease
- Patients with cardiac allograft vasculopathy
Anatomical settings
- Vulnerable plaques
- Thrombotic lesions
- Left main coronary artery disease
- Bifurcation lesions
- Saphenous vein grafts
- Chronic total occlusions
- Calcified lesions
- Aneurysmatic coronary artery disease

TABLE 14. TASK FORCE RECOMMENDED ENDPOINTS FOR TRIALS OF CORONARY STENTS

Safety endpoints - Death - Cardiac death - Myocardial infarction - Definite stent thrombosis
Efficacy endpoints - Any coronary revascularization - Target vessel revascularization - Target lesion revascularization
Composite efficacy and safety - Cardiac death, target vessel myocardial infarction and target lesion revascularization (device-oriented) - All-cause death, any myocardial infarction and any revascularization (patient-oriented)

11. FIGURE LEGENDS

FIGURE 1. ACTUAL AND ESTIMATED USE OF CORONARY STENTS (2010-2017)

This figures summarizes the actual as well as estimated worldwide use of coronary stents classified according to type into bare metal stents (orange), drug-eluting stents (purple) and bioresorbable stents (green). Estimates are based on previous experience with early generation drug-eluting stent market penetration. Source: JP Morgan.

FIGURE 2. ITERATIVE DEVELOPMENT AND TECHNOLOGICAL PROGRESS OF DRUG-ELUTING STENTS: OVERVIEW OF EARLY AND NEW GENERATION DEVICES

This figure provides an overview of the technological progess with drug-eluting stents since their introduction up to date with important changes in strut thickness, biocompatibility of durable and biodegradable polymers and antiproliferative drug release. SS denotes stainless steel; CoCr, cobalt chromium; PtCr, platinum chromium; SIBS, poly(styrene-b-isobutylene-b-styrene); PEVA, poly ethylene-co-vinyl acetate; PBMA, poly n-butyl methacrylate; PVDF-HFP, co-polymer of vinylidene fluoride and hexafluoropropylene; MPC, methacryloyloxyethyl phosphorylcholine; LMA, lauryl methacrylate; HPMA, hydroxypropyl methacrylate; 3-MPMA, trimethoxysilylpropyl methacrylate; PVP, polyvinyl pyrrolidinone; PHMA, polyhexyl methacrylate; PVA, polyvinyl acetate; PLGA, poly-lactic co-glycolic acid; PLLA, poly-L-lactic acid; PDLLA, poly-D, L-lactic acid.
(Adapted from Stefanini GG et al. *Heart* 2014; 100:1051-61)

FIGURE 3. SUMMARY OF CORONARY STENT APPROVAL PATHWAYS IN EUROPE AND IN THE UNITED STATES

This figure shows the pathway of approval related to coronary stents and major prerequisites to be fulfilled at various time points in Europe (top) and USA (bottom).
IDE denotes Investigational Device Exemption; PMA, premarket approval; OUS, out of United States

FIGURE 4. SYSTEMATIC REVIEW - SUMMARY OF ABSTRACT AND FULL-TEXT SCREENING

Flow-diagram summary of the abstract and full-text screening process for the systematic review of coronary stents.

FIGURE 5. SYSTEMATIC REVIEW RESULTS: CLINICAL OUTCOMES AT 9-12 MONTHS - MEDIAN RATES PER 100 PERSON YEARS

Median rates per 100 person year for the clinical endpoints all-cause death, myocardial infarction, target-lesion revascularization, and definite stent thrombosis per 100 person years.

BMS denotes bare metal stents; DES, drug-eluting stents

FIGURE 6. SYSTEMATIC REVIEW RESULTS: MEDIAN CUMULATIVE FREQUENCY OF IN-STENT LATE LUMEN LOSS

BMS denotes bare metal stents; DES, drug-eluting stents

FIGURE 7. RISK OF ALL-CAUSE MORTALITY WITH DIFFERENT REVASCULARIZATION STRATEGIES COMPARED WITH MEDICAL THERAPY IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE.

Adapted from Windecker S et al. BMJ 2014

FIGURE 8. ENDPOINT MODEL CLAIMS AND INTENDED USE

FIGURE 9. PRODUCT LIFE CYCLE

Adapted from Chen E et al. Ann Thorac Surg 2006;82:773–5.

FIGURE 10. PROPOSED CLINICAL DEVELOPMENT PLAN

Proposed clinical development plan from non-clinical evaluation to post-market surveillance.

OPC denotes optimal performance criteria.

FIGURE 11. NOMOGRAM FOR IN-STENT LATE LUMEN LOSS OPTIMAL PERFORMANCE CRITERIA CALCULATION

12. FIGURES

FIGURE 1. ACTUAL AND ESTIMATED USE OF CORONARY STENTS (2010-2017)

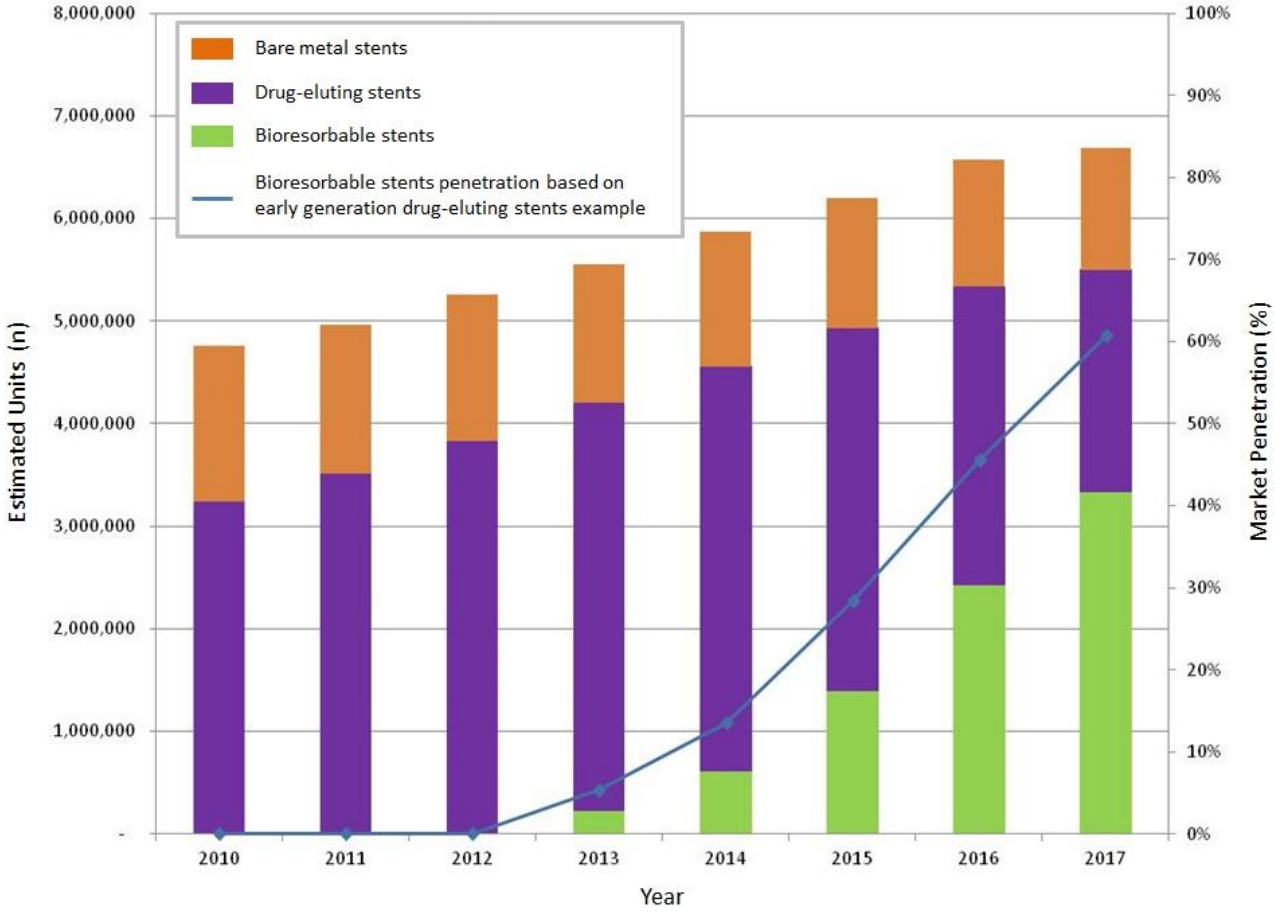
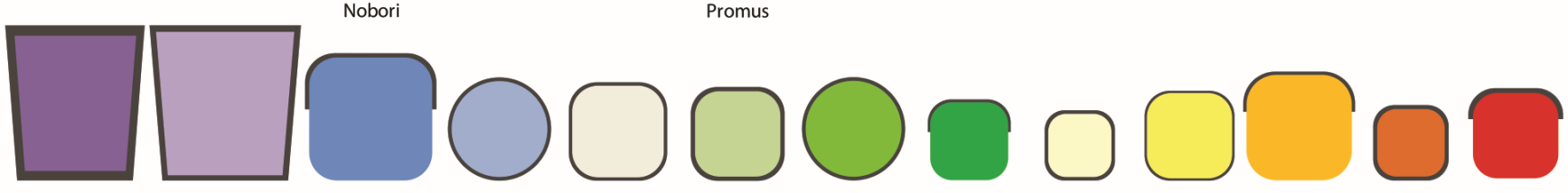


FIGURE 2. ITERATIVE DEVELOPMENT AND TECHNOLOGICAL PROGRESS OF DRUG-ELUTING STENTS: OVERVIEW OF EARLY AND NEW GENERATION DEVICES



	Taxus	Cypher	BioMatrix Nobori	Endeavor	Yukon PC	Xience Promus	Resolute	Synergy	Orsiro	DESyne	Combo	Mistent	Ultimaster
Platform material	SS	SS	SS	CoCr	SS	CoCr PtCr	CoCr	PtCr	CoCr	CoCr	SS	CoCr	CoCr
Strut thickness (µm)	132	140	120	91	87	81	91	74	60	81	100	64	80
Polymer type	Durable	Durable	Biodegradable	Durable	Biodegradable	Durable	Durable	Biodegradable	Biodegradable	Biodegradable	Biodegradable	Biodegradable	Biodegradable
Polymer material	SIBS	PEVA/PBMA	PDLLA	MPC/LMA/HPMA/ 3-MPMA	PDLLA	PBMA/PVDF-HFP	PBMA/PHMA/ PVP/PVA	PLGA	PLLA	PLLA	PDLLA/PLGA	PLGA	PDLLA-PCL
Coating distribution	Circumferential	Circumferential	Abluminal	Circumferential	Circumferential	Circumferential	Circumferential	Abluminal	Circumferential	Circumferential	Abluminal	Circumferential	Abluminal
Polymer thickness (µm)	22	13	10	6	5	8	6	4	7	<3	5	10	15
Additional coating	-	-	-	-	-	-	-	-	Silicon carbide	-	Anti-CD34 Antibodies	-	-
Drug released	Paclitaxel	Sirolimus	Biolimus	Zotarolimus	Sirolimus	Everolimus	Zotarolimus	Everolimus	Sirolimus	Novolimus	Sirolimus	Sirolimus	Sirolimus

FIGURE 3. SUMMARY OF CORONARY STENT APPROVAL PATHWAYS IN EUROPE AND IN THE UNITED STATES

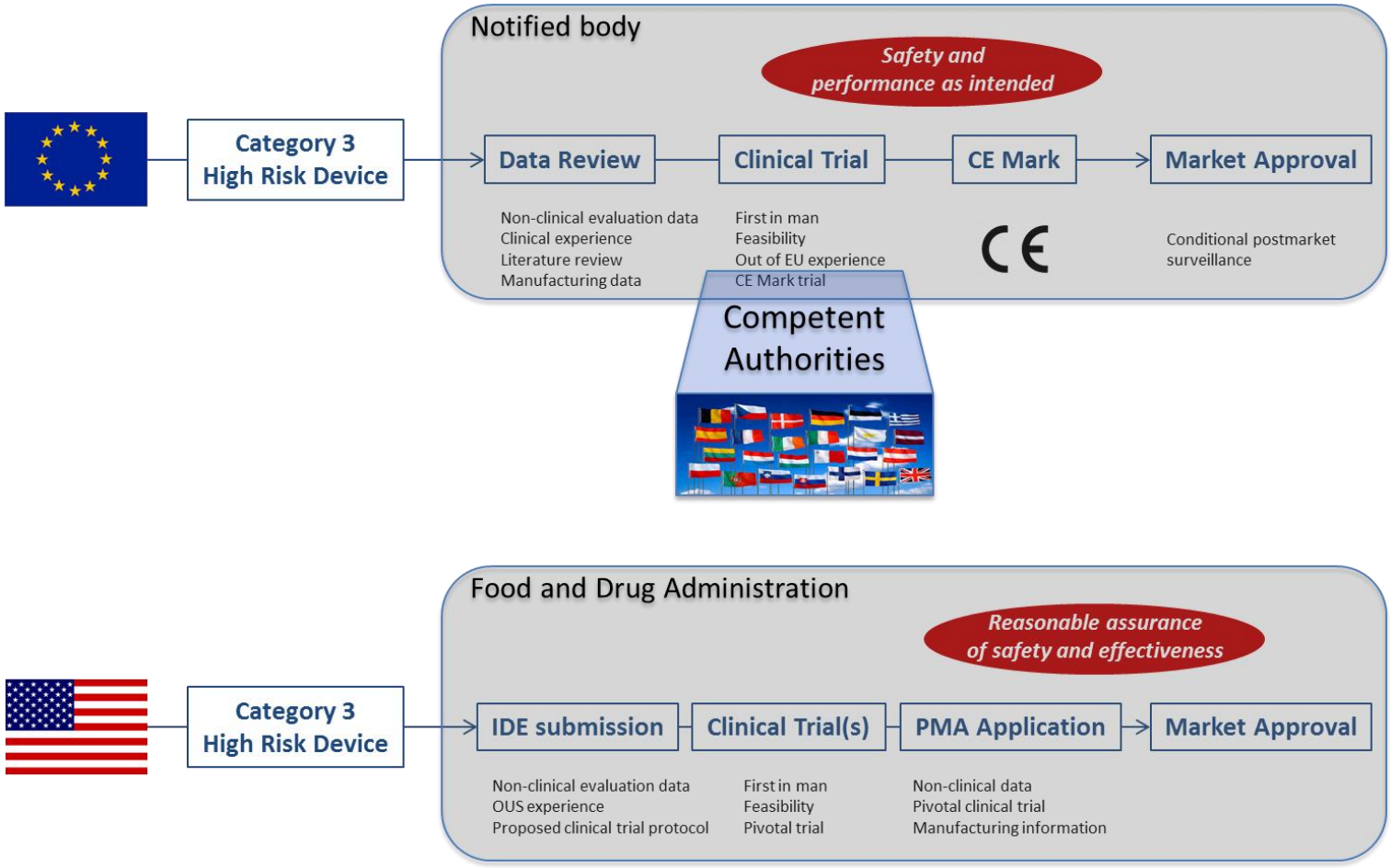


FIGURE 4. SYSTEMATIC REVIEW - SUMMARY OF ABSTRACT AND FULL-TEXT SCREENING

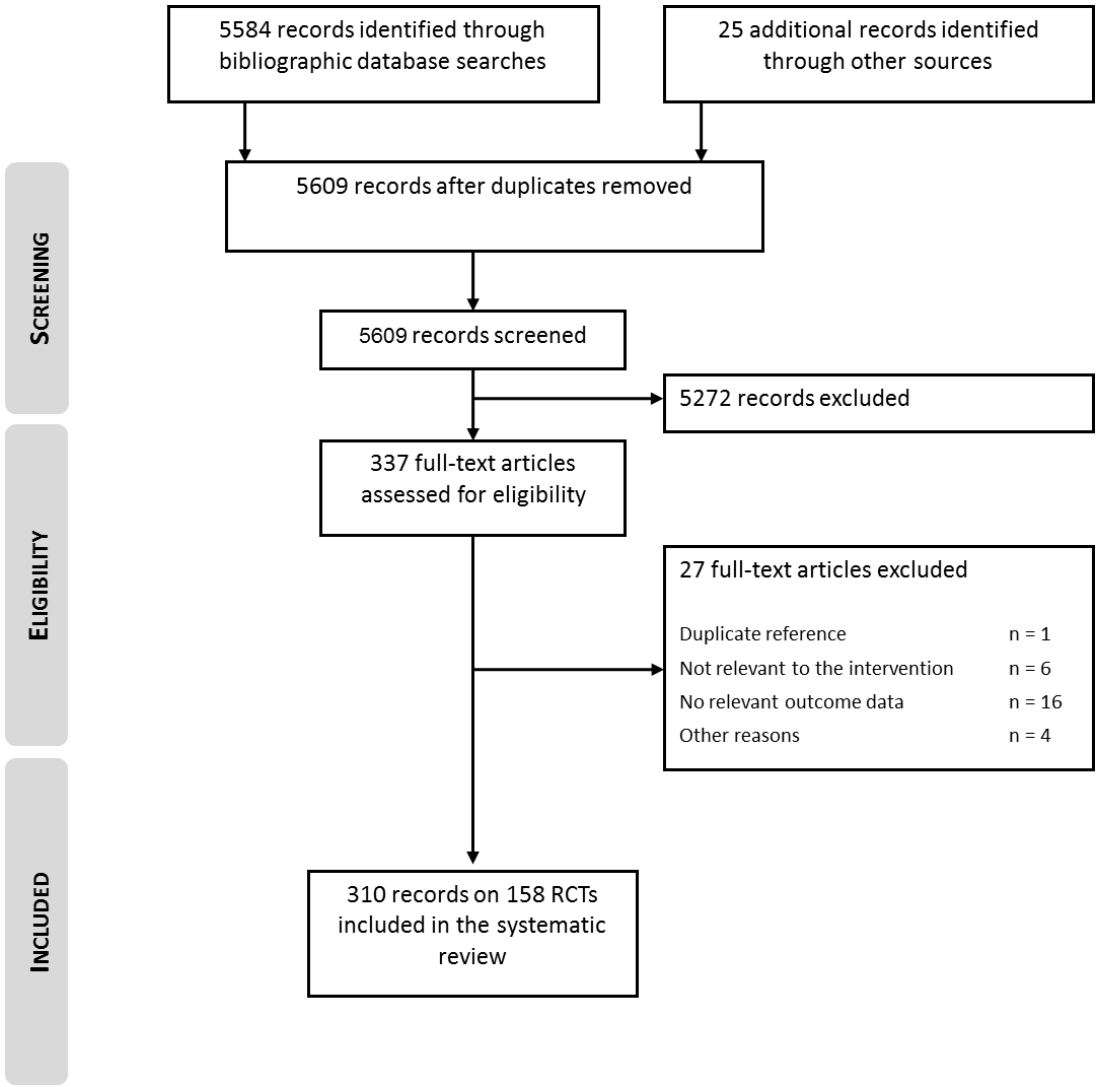


FIGURE 5. SYSTEMATIC REVIEW RESULTS: CLINICAL OUTCOMES AT 9-12 MONTHS - MEDIAN RATES PER 100 PERSON YEARS

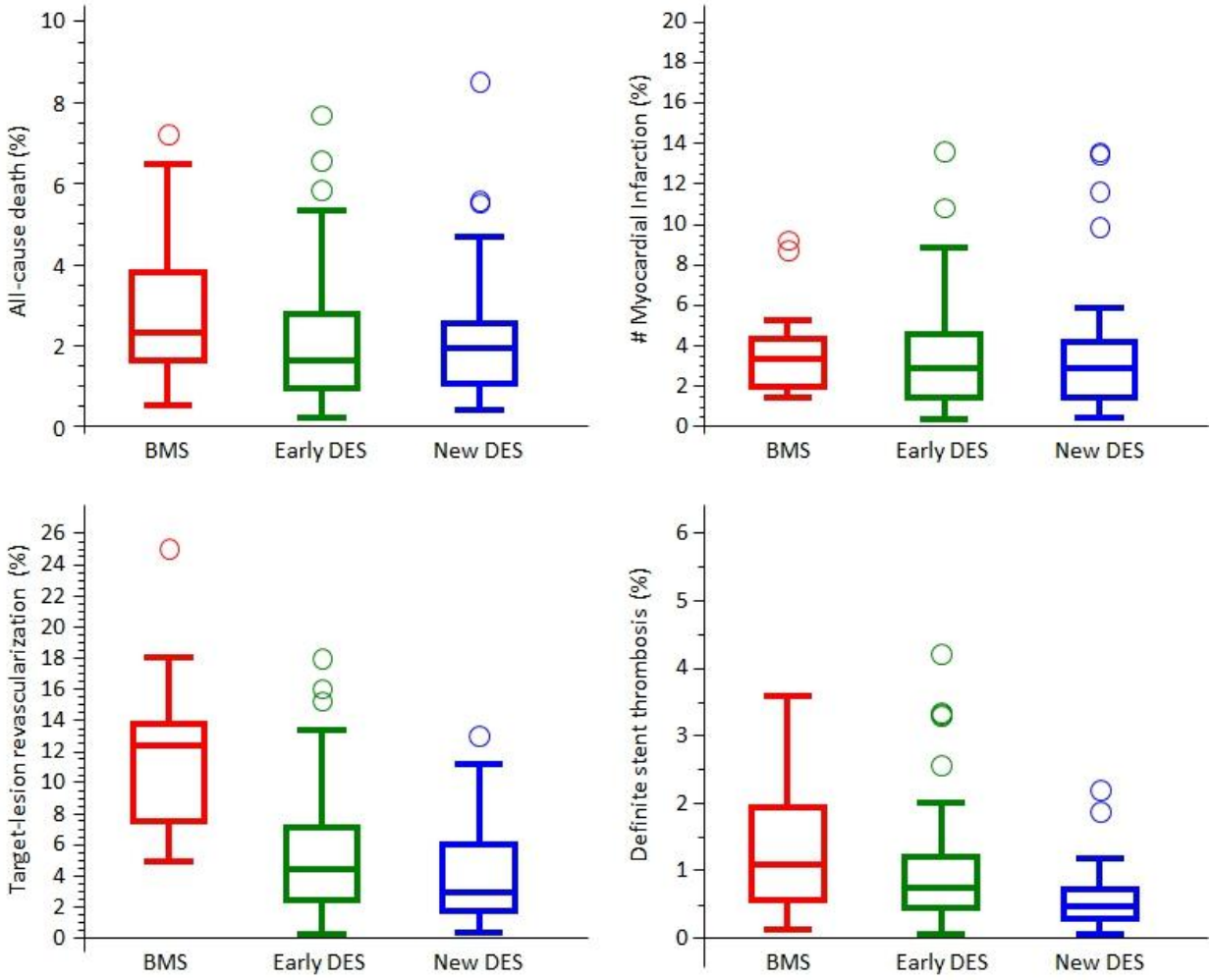


FIGURE 6. SYSTEMATIC REVIEW RESULTS: MEDIAN CUMULATIVE FREQUENCY OF IN-STENT LATE LUMEN LOSS

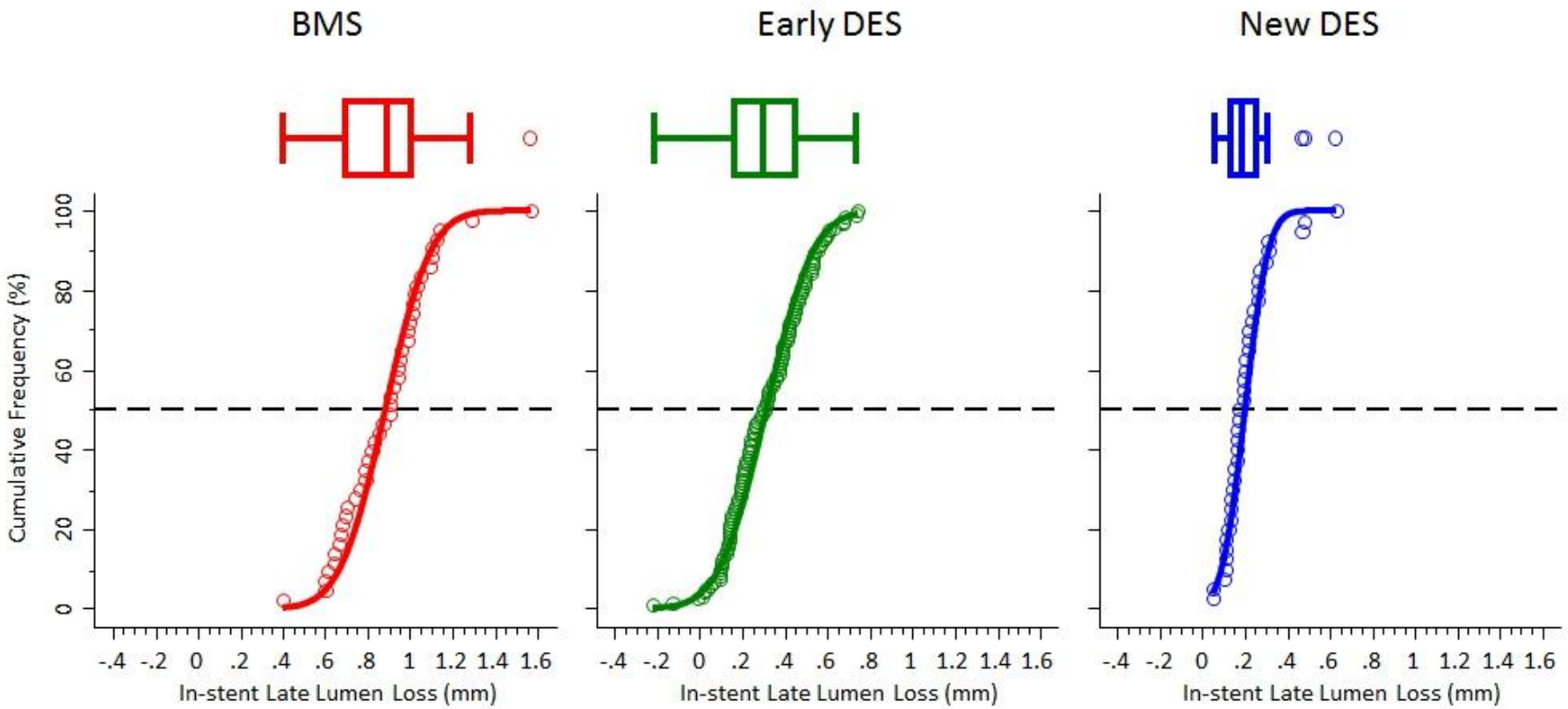


FIGURE 7. RISK OF ALL-CAUSE MORTALITY WITH DIFFERENT REVASCULARIZATION STRATEGIES COMPARED WITH MEDICAL THERAPY IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE.

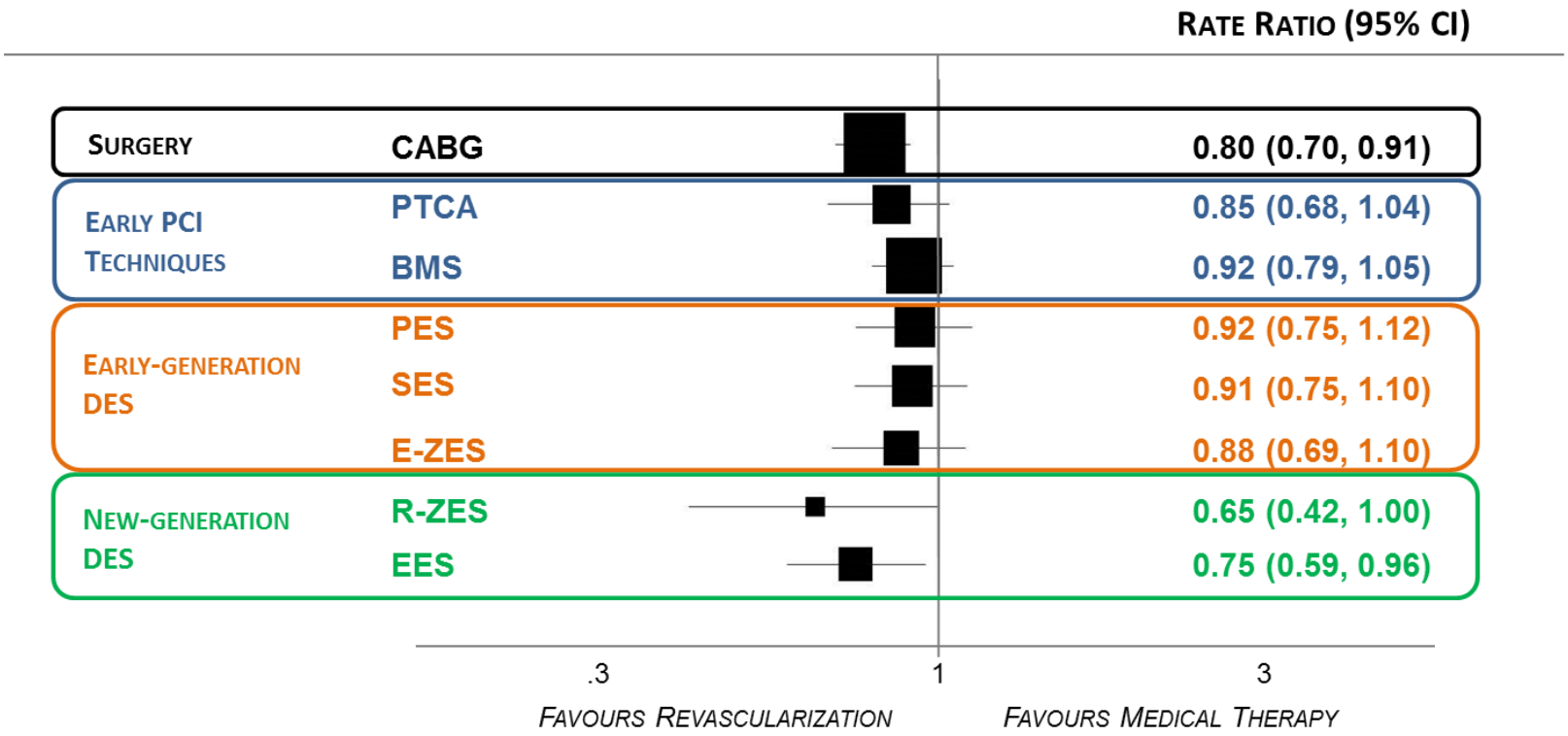


FIGURE 8. ENDPOINT MODEL CLAIMS AND INTENDED USE

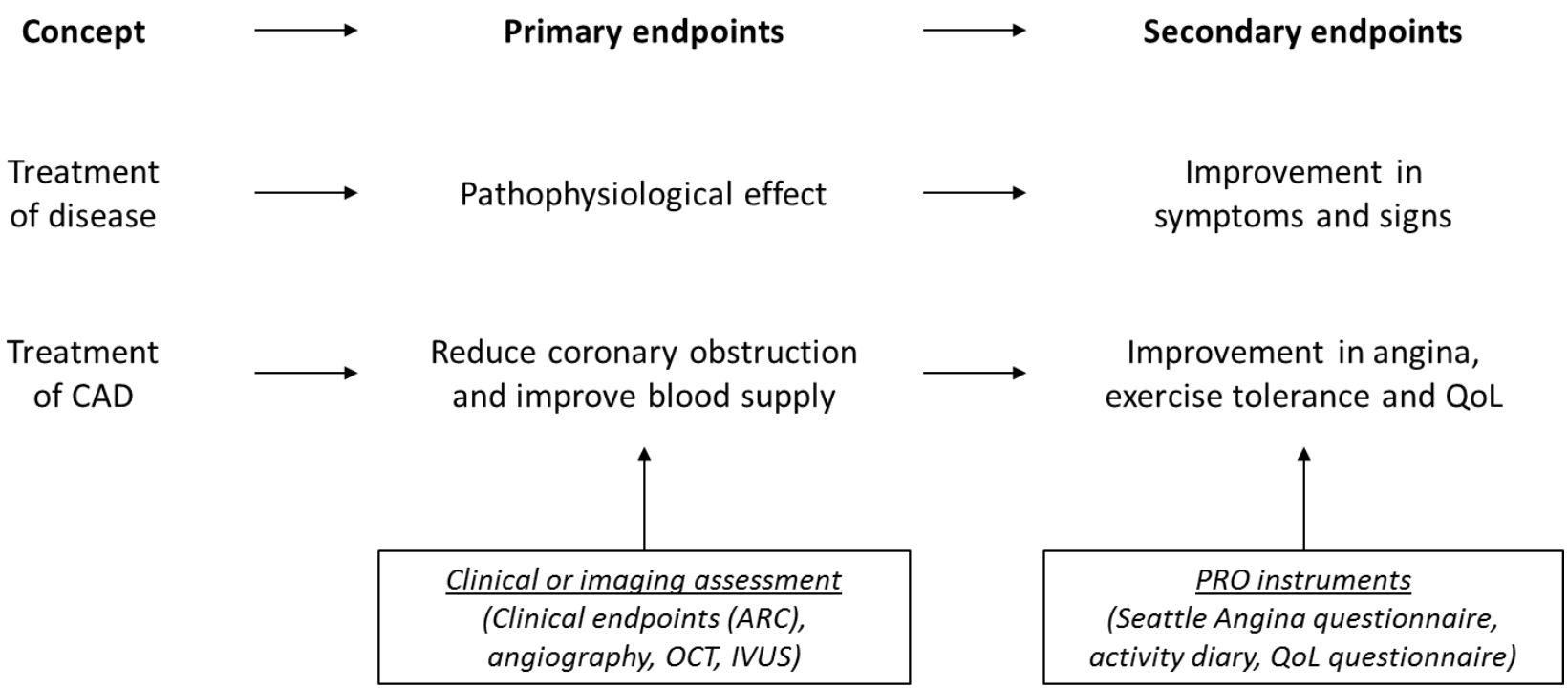


FIGURE 9. PRODUCT LIFE CYCLE

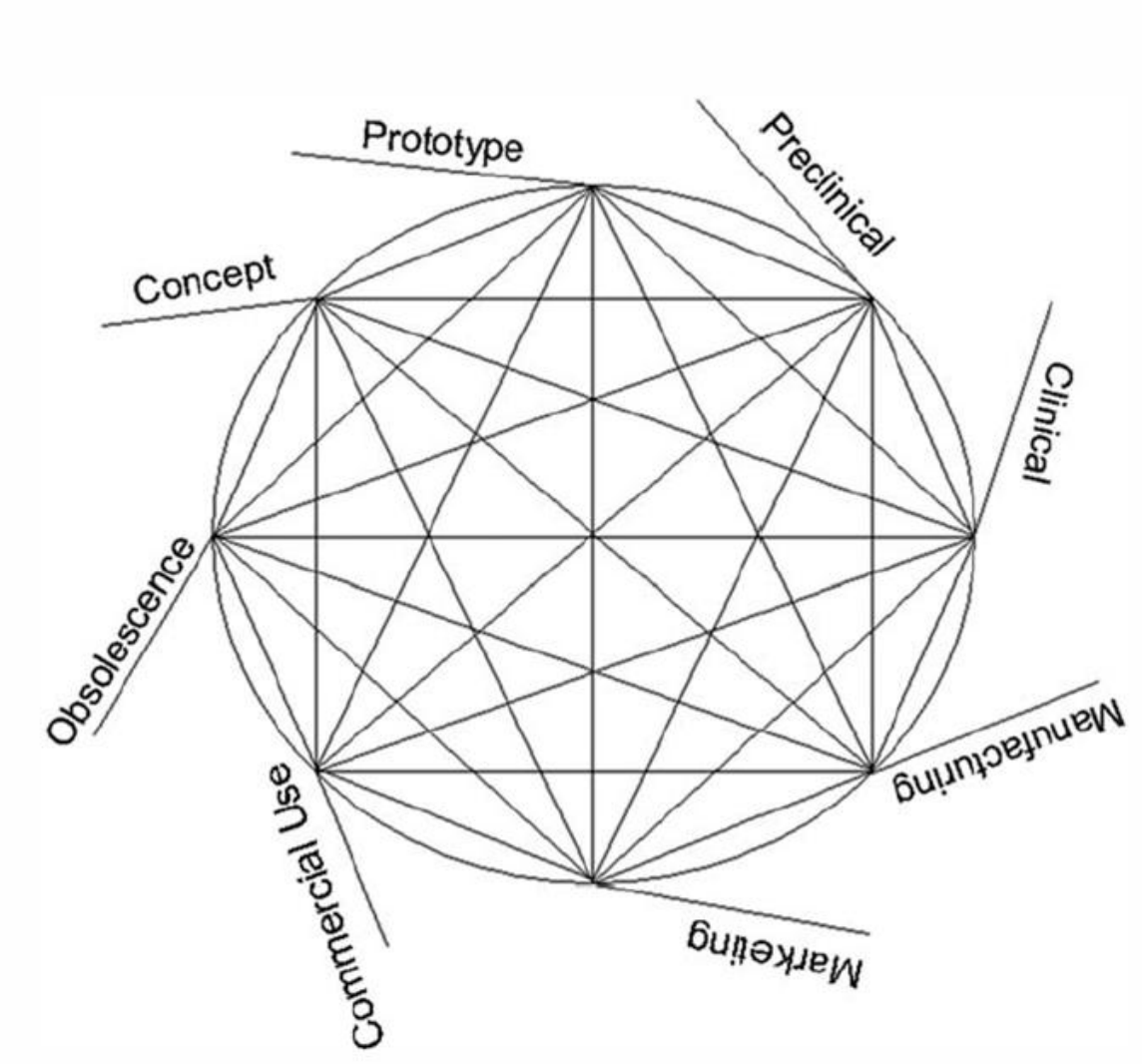


FIGURE 10. PROPOSED CLINICAL DEVELOPMENT PLAN

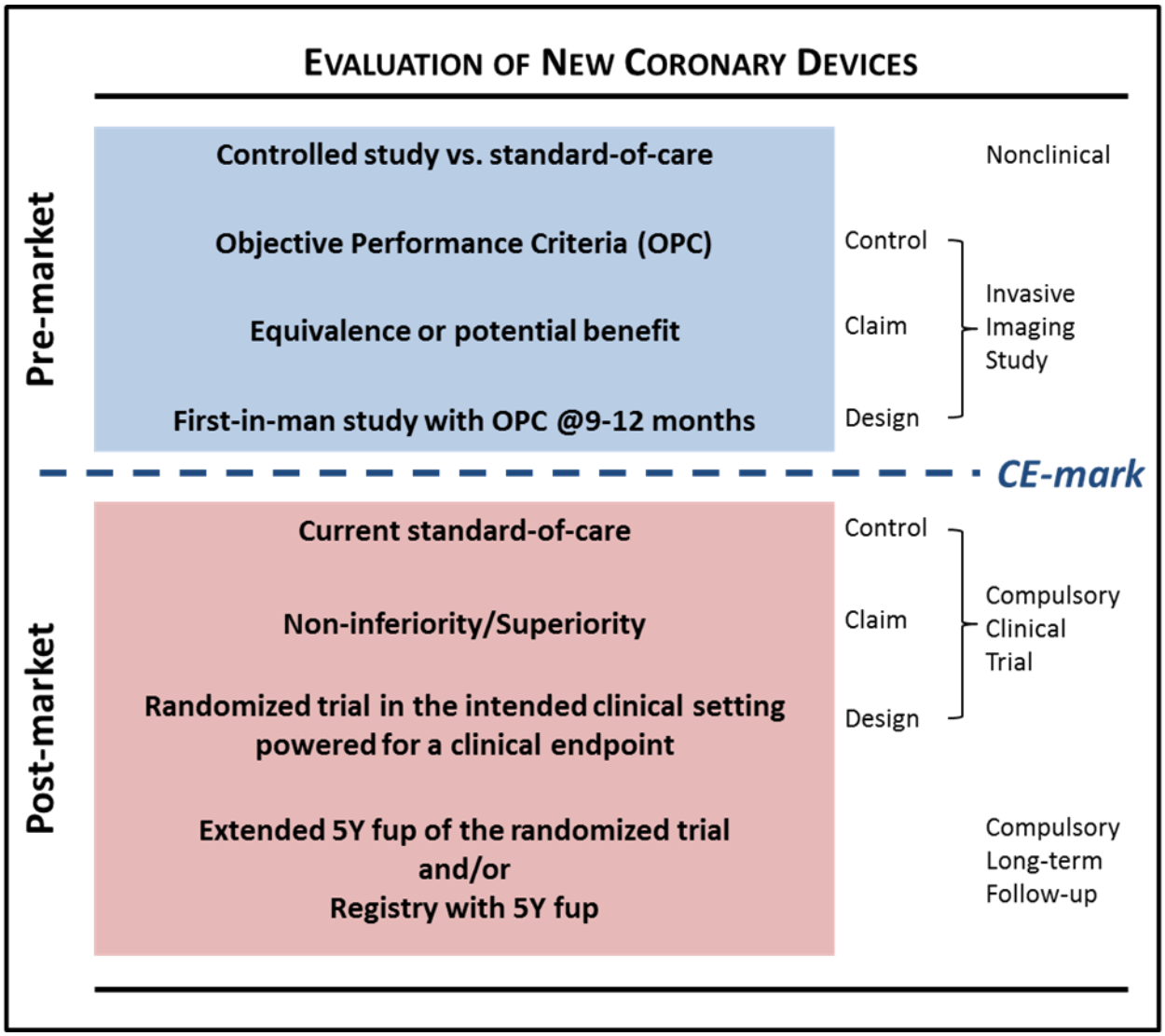
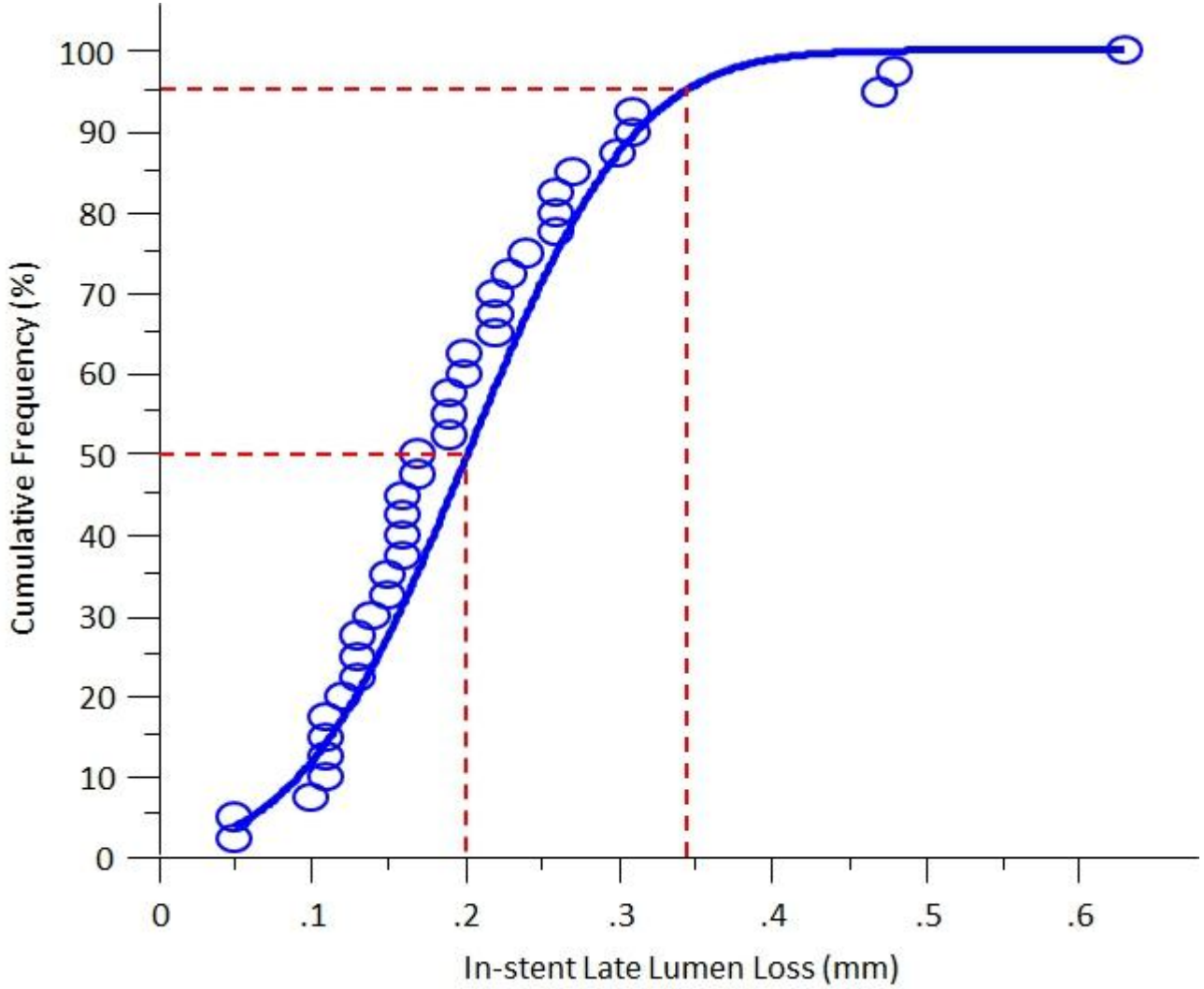


FIGURE 11. NOMOGRAM FOR IN-STENT LATE LUMEN LOSS OPTIMAL PERFORMANCE CRITERIA CALCULATION



SUPPLEMENTAL TABLES - SYSTEMATIC REVIEW

TABLE S1. TRIALS AND STENTS CHARACTERISTICS

	Total nr of Trials / Arms N = 158 / n = 333		Total nr of Patients N = 108839	
	Nr of contributing trials	N of trials (%)	Nr of contributing patients[a]	N of patients (%)[a]
Trial Characteristics				
Year of study publication (range)*	158	2003-2014		
Number of treatment arms compared	158		108839	
Two arms		142 (89.9%)		95555 (87.8%)
Three arms		15 (9.5%)		11271 (10.4%)
Four arms		1 (0.6%)		2013 (1.8%)
N of trials comparing DES vs. BMS	158	59 (37.3%)	108839	29951 (27.5%)
N of trials comparing DES vs. DES	158	103 (65.2%)	108839	84473 (77.6%)
N of trials with Clinical Follow-up time reported	158	157 (99.4%)	108839	108539 (99.7%)
N of trials with Clinical Primary Endpoint reported	158	58 (36.7%)	108839	74505 (68.5%)
N of trials with any Clinical Outcome reported	158	150 (94.9%)	108839	107327 (98.6%)
N of trials with Angiographic Follow-up time reported	158	121 (76.6%)	108839	61831 (56.8%)
N of trials with Angiographic Primary Endpoint reported	158	64 (40.5%)	108839	23940 (22.0%)
N of trials with any Angiographic Outcome reported	158	121 (76.6%)	108839	61831 (56.8%)
N of multicenter studies	158		108839	
single-center		35 (22.2%)		11366 (10.4%)
multi-center		113 (71.5%)		94766 (87.1%)
unclear		10 (6.3%)		2707 (2.5%)
Geographic location of recruiting sites	158		108839	
Europe		82 (51.9%)		50358 (46.3%)
North America		9 (5.7%)		11636 (10.7%)
Europe and North America		1 (0.6%)		80 (0.1%)
Various other locations		56 (35.4%)		45403 (41.7%)
Unclear locations		10 (6.3%)		1362 (1.3%)
Mean N of patients per trial (range)‡	158	688.9 (30-8709)		
N of studies with >100 patients	158	135 (85.4%)	108839	107270 (98.6%)
N of studies with >1000 patients	158	33 (20.9%)	108839	69933 (64.3%)
N of studies with ITT analysis**	81	50 (61.7%)	91407	63165 (69.1%)
N of studies with ITT or modified ITT analysis**	81	68 (84.0%)	91407	83622 (91.5%)

N of studies with adequate concealment of allocation	158	62 (39.2%)	108839	70403 (64.7%)
N of studies with any blinded CEC or independent core-lab Adjudication	158	120 (75.9%)	108839	95937 (88.1%)
of clinical events by blinded CEC	158	93 (58.9%)	108839	86460 (79.4%)
of angio endpoints by independent core-lab	158	79 (50.0%)	108839	48191 (44.3%)
N of studies with commercial funding	158	78 (49.4%)	108839	74184 (68.2%)
Drug-Eluting Stents Investigated				
Nr of DES investigated	158	32		
Types of DES investigated¶	156	in 270 DES arms	97690	
Amazonia PAX		1 (0.6%)		15 (0.0%)
BioFreedom		2 (1.3%)		122 (0.1%)
BioMatrix		4 (2.6%)		1615 (1.7%)
Combo		1 (0.6%)		124 (0.1%)
Coracto SES		1 (0.6%)		48 (0.0%)
Coroflex Please PES		2 (1.3%)		790 (0.8%)
Cre8		1 (0.6%)		162 (0.2%)
Cypher		87 (55.8%)		27254 (27.9%)
DESyne BD		1 (0.6%)		75 (0.1%)
DESyne Nx		1 (0.6%)		139 (0.1%)
Endeavor		21 (13.5%)		10436 (10.7%)
Eucatax PES		1 (0.6%)		211 (0.2%)
Firebird		1 (0.6%)		224 (0.2%)
Infinnium		1 (0.6%)		111 (0.1%)
Janus		2 (1.3%)		266 (0.3%)
Luc Chopin 2		1 (0.6%)		25 (0.0%)
Nevo		1 (0.6%)		202 (0.2%)
Nobori		7 (4.5%)		5092 (5.2%)
Pico Elite PES		1 (0.6%)		20 (0.0%)
Promus Element		3 (1.9%)		1016 (1.0%)
Resolute		8 (5.1%)		3840 (3.9%)
SimvES		1 (0.6%)		14 (0.0%)
Supralimus		1 (0.6%)		106 (0.1%)
Synergy		2 (1.3%)		193 (0.2%)
Taxus		68 (43.6%)		19143 (19.6%)
Taxus Element		1 (0.6%)		942 (1.0%)
Xience		20 (12.8%)		5425 (5.6%)
Xience/Promus		17 (10.9%)		14296 (14.6%)
Yukon Choice PC		2 (1.3%)		1501 (1.5%)

Yukon Choice PF	6 (3.8%)	2907 (3.0%)
ZoMaxx	2 (1.3%)	760 (0.8%)

Data reported as nr of trials (% of total nr of trials) and total nr of patients (% of total nr of patients), except *year of study publication with range, ¶DES stents per nr of arms out of 270 DES arms investigated in 156 trials in 97690 patients, and ǂmean number of patients per trial with range.

DES were used in 270 arms in 156 trials; BMS were used in 63 arms in 61 trials, meaning that in two trials BMS was compared with another type of BMS head-to-head (no DES arms).

** For the primary clinical endpoint of each study, missing for non-full paper reports and missing for studies with a primary angiographic endpoint reported only.

[a] Throughout it was assumed that the nr of patients randomized was the total nr randomized divided by nr of arms (rounded), in case the nr randomized per arm was not extractable.

TABLE S2. PATIENTS CHARACTERISTICS

	Nr of contributing trials*	Mean ± SD	Median (IQR)	Range	Nr of contributing patients	Nr of patients with characteristics (%)
Mean Age (years)	152	63.66 ± 3.19	63.16 (61.95-65.01)	55.49-83.50	106917	
Female patients	149	25.23 ± 6.96	24.92 (21.11-28.42)	0.00-48.48	107375	27743 (25.8%)
Diabetics	149	32.80 ± 25.15	25.34 (19.04-32.14)	0.00-100.00	106231	29173 (27.5%)
Stable CAD	100	41.66 ± 30.48	42.13 (10.49-64.32)	0.00-100.00	82909	36942 (44.6%)
Unstable angina	112	23.09 ± 18.98	21.68 (0.00-34.61)	0.00-77.27	87609	19513 (22.3%)
NSTEMI	93	5.47 ± 12.39	0.00 (0.00-0.00)	0.00-59.52	67089	5493 (8.2%)
STEMI	109	25.93 ± 40.38	0.00 (0.00-32.19)	0.00-100.00	79367	20318 (25.6%)
Multivessel disease	111	44.24 ± 26.33	45.00 (26.67-61.04)	0.00-124.04	90974	36080 (39.7%)
Left Main disease	105	3.89 ± 16.71	0.00 (0.00-1.40)	0.00-100.00	84579	2419 (2.9%)
Bifurcation lesions	74	23.04 ± 26.98	17.05 (5.67-26.92)	0.00-100.00	66623	14103 (21.2%)
Bypass lesions	70	6.16 ± 23.29	0.00 (0.00-0.48)	0.00-100.00	58737	1206 (2.1%)
In-stent restenosis lesions	96	3.96 ± 17.51	0.00 (0.00-0.00)	0.00-100.00	66368	2317 (3.5%)
Chronic total occlusion lesions	62	15.63 ± 31.04	3.96 (0.00-9.00)	0.00-100.00	63669	4308 (6.8%)

*Total N of trials=158

Data reported as number of trials (% total nr of trials), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients); count of patients in the respective category (% nr of contributing patients).

CAD=coronary artery disease; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction

TABLE S3. DEDICATED TRIALS TO SPECIFIC PATIENTS AND LESIONS SUBSETS

	Number of trials		Number of patients
	with available info	performed in subset (%)	included
N of trials on specific patients subsets*			
All comers	156	19 (12.03%)	40052
STEMI	109	20 (12.66%)	12434
Diabetes	149	16 (10.13%)	3380
Female patients	149	0 (0.00%)	0
Elderlies (mean age ≥75 years)	152	1 (0.63%)	800
N of trials on specific lesions subsets*			
Multivessel disease	111	3 (1.90%)	1226
Left main disease	105	3 (1.90%)	1360
Saphenous vein graft lesions	70	4 (2.53%)	816
In-stent restenosis lesions	96	3 (1.90%)	716
Bifurcation lesions	74	6 (3.80%)	1568
Chronic total occlusions	62	6 (3.80%)	911

Data reported as number of trials conducted within the specified patient or lesion population (% total number of trials).
*100% of the randomized patients fall into the category indicated.

TABLE S4. PATIENT CHARACTERISTICS BY STENT GROUP

	Nr of contributing trials	Mean ± SD	Median (IQR)	Range	Nr of contributing patients	Nr of patients with characteristics (%)
BMS (any)						
Mean Age (years)	10	65.99 ± 7.21	63.92 (63.00-65.50)	57.00-83.50	3700	
Female patients	9	23.53 ± 7.44	23.94 (19.87-24.94)	14.67-39.88	3527	956 (27.1%)
Diabetics	10	28.23 ± 25.61	19.97 (16.93-24.88)	14.50-100.00	3700	851 (23.0%)
Stable CAD	5	16.93 ± 24.30	0.00 (0.00-32.00)	0.00-52.65	2372	415 (17.5%)
Unstable angina	8	20.52 ± 26.59	11.80 (0.00-36.29)	0.00-68.00	3467	761 (21.9%)
NSTEMI	7	20.37 ± 26.07	0.00 (0.00-47.52)	0.00-57.65	3274	751 (22.9%)
STEMI	8	36.40 ± 42.77	24.41 (0.00-71.18)	0.00-100.00	3225	1352 (41.9%)
Multivessel disease	6	31.00 ± 18.61	32.33 (24.50-43.29)	0.00-53.56	2447	981 (40.1%)
Left Main disease	5	2.09 ± 3.33	0.94 (0.48-1.04)	0.00-8.00	2990	77 (2.6%)
Bifurcation lesions	4	40.81 ± 39.55	22.82 (19.51-62.12)	17.62-100.00	1505	374 (24.9%)
Bypass lesions	4	26.30 ± 49.15	2.46 (1.28-51.31)	0.27-100.00	2447	117 (4.8%)
In-stent restenosis lesions	6	0.56 ± 1.37	0.00 (0.00-0.00)	0.00-3.36	2325	25 (1.1%)
Chronic total occlusion lesions	2	13.99 ± 19.78	13.99 (0.00-27.98)	0.00-27.98	268	54 (20.1%)
DES (any)						
Mean Age (years)	142	63.50 ± 2.68	63.08 (61.85-64.92)	55.49-71.45	103217	
Female patients	140	25.29 ± 7.08	24.97 (21.21-28.90)	0.00-48.48	103848	26784 (25.8%)
Diabetics	139	33.25 ± 25.13	25.91 (19.24-33.33)	0.00-100.00	102531	28330 (27.6%)
Stable CAD	96	43.50 ± 30.25	43.99 (17.22-64.67)	0.00-100.00	80837	36730 (45.4%)
Unstable angina	105	23.33 ± 18.34	23.36 (5.73-34.01)	0.00-77.27	84442	18836 (22.3%)
NSTEMI	87	4.21 ± 9.87	0.00 (0.00-0.00)	0.00-59.52	64115	4742 (7.4%)
STEMI	102	24.86 ± 40.18	0.00 (0.00-25.67)	0.00-100.00	76442	18966 (24.8%)
Multivessel disease	105	45.00 ± 26.57	46.63 (27.57-61.39)	0.00-124.04	88527	35099 (39.6%)
Left Main disease	100	3.98 ± 17.11	0.00 (0.00-1.40)	0.00-100.00	81589	2342 (2.9%)
Bifurcation lesions	70	22.03 ± 26.13	15.53 (0.00-26.92)	0.00-100.00	65118	13729 (21.1%)
Bypass lesions	66	4.94 ± 20.93	0.00 (0.00-0.41)	0.00-100.00	56290	1089 (1.9%)
In-stent restenosis lesions	90	4.19 ± 18.07	0.00 (0.00-0.00)	0.00-100.00	64043	2292 (3.6%)
Chronic total occlusion lesions	60	15.68 ± 31.46	3.96 (0.00-8.75)	0.00-100.00	63401	4254 (6.7%)
Early DES						
Mean Age (years)	82	63.01 ± 2.72	62.55 (61.00-64.50)	55.49-70.00	48563	
Female patients	81	24.46 ± 7.94	23.70 (20.00-27.96)	0.00-48.48	49224	12502 (25.4%)
Diabetics	79	35.46 ± 28.13	26.71 (18.35-36.00)	0.00-100.00	47877	13071 (27.3%)

Stable CAD	61	42.70 ± 32.29	42.50 (0.00-65.99)	0.00-100.00	40890	16953 (41.5%)
Unstable angina	55	21.37 ± 21.33	18.81 (0.00-36.75)	0.00-77.27	37071	8282 (22.3%)
NSTEMI	48	2.20 ± 7.11	0.00 (0.00-0.00)	0.00-34.62	33736	2007 (5.9%)
STEMI	59	32.33 ± 45.38	0.00 (0.00-100.00)	0.00-100.00	38270	11350 (29.7%)
Multivessel disease	60	49.48 ± 23.94	47.93 (39.19-64.30)	0.00-124.04	42689	15653 (36.7%)
Left Main disease	52	4.79 ± 19.38	0.00 (0.00-1.14)	0.00-100.00	34423	1040 (3.0%)
Bifurcation lesions	35	26.24 ± 31.16	18.58 (0.00-33.85)	0.00-100.00	26566	5919 (22.3%)
Bypass lesions	41	5.22 ± 21.76	0.00 (0.00-0.00)	0.00-100.00	28811	261 (0.9%)
In-stent restenosis lesions	48	6.56 ± 24.40	0.00 (0.00-0.00)	0.00-100.00	28547	919 (3.2%)
Chronic total occlusion lesions	30	23.84 ± 39.39	3.19 (0.00-16.37)	0.00-100.00	24437	1971 (8.1%)
New DES						
Mean Age (years)	42	64.39 ± 2.38	63.80 (63.00-66.10)	59.60-69.20	48113	
Female patients	42	26.51 ± 5.32	26.37 (23.11-29.82)	14.71-41.00	48113	12490 (26.0%)
Diabetics	42	32.16 ± 23.65	26.55 (20.00-29.56)	9.76-100.00	48113	13531 (28.1%)
Stable CAD	29	44.50 ± 27.21	48.44 (29.32-64.00)	0.00-100.00	37887	18940 (50.0%)
Unstable angina	38	23.99 ± 13.57	23.87 (16.67-30.91)	0.00-64.00	41744	8832 (21.2%)
NSTEMI	26	6.56 ± 9.50	0.00 (0.00-11.76)	0.00-28.18	24758	2514 (10.2%)
STEMI	30	16.42 ± 29.82	0.00 (0.00-20.98)	0.00-100.00	32551	6899 (21.2%)
Multivessel disease	31	44.42 ± 26.91	47.36 (22.75-58.81)	0.00-100.00	39893	17457 (43.8%)
Left Main disease	35	4.09 ± 16.81	0.17 (0.00-2.00)	0.00-100.00	41944	1278 (3.0%)
Bifurcation lesions	27	20.09 ± 20.57	15.50 (7.50-26.02)	0.00-100.00	35787	7542 (21.1%)
Bypass lesions	20	0.59 ± 0.90	0.03 (0.00-0.90)	0.00-2.52	25694	218 (0.8%)
In-stent restenosis lesions	26	2.38 ± 4.15	0.00 (0.00-3.99)	0.00-13.72	30104	1373 (4.6%)
Chronic total occlusion lesions	24	4.52 ± 4.45	4.53 (0.00-7.61)	0.00-16.62	36977	2091 (5.7%)
FDA approved New DES						
Mean Age (years)	28	63.95 ± 2.21	63.30 (63.00-64.75)	59.60-69.10	31686	
Female patients	28	27.19 ± 5.49	26.90 (23.15-30.02)	16.89-41.00	31686	8517 (26.9%)
Diabetics	28	32.46 ± 25.06	26.58 (18.65-30.82)	9.76-100.00	31686	8844 (27.9%)
Stable CAD	22	41.10 ± 25.24	40.89 (22.00-62.00)	0.00-81.63	27922	13650 (48.9%)
Unstable angina	25	26.43 ± 13.79	26.00 (19.15-33.20)	0.00-64.00	27785	6340 (22.8%)
NSTEMI	15	7.66 ± 9.84	4.00 (0.00-15.33)	0.00-28.18	17036	1496 (8.8%)
STEMI	18	18.73 ± 31.17	1.56 (0.00-25.67)	0.00-100.00	22361	4443 (19.9%)
Multivessel disease	21	45.17 ± 25.06	47.66 (24.95-55.56)	0.00-100.00	27785	11554 (41.6%)
Left Main disease	21	6.45 ± 21.57	0.66 (0.00-2.59)	0.00-100.00	25517	1076 (4.2%)
Bifurcation lesions	18	21.21 ± 23.54	14.23 (8.17-26.02)	0.00-100.00	20542	4017 (19.6%)
Bypass lesions	16	0.57 ± 0.84	0.03 (0.00-0.90)	0.00-2.44	21981	173 (0.8%)
In-stent restenosis lesions	13	2.96 ± 4.62	0.00 (0.00-4.96)	0.00-13.72	17106	764 (4.5%)
Chronic total occlusion lesions	14	4.50 ± 4.66	4.53 (0.00-6.83)	0.00-16.62	22530	1120 (5.0%)

Data reported as number of trials (% total nr of trials), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients).

CAD=coronary artery disease; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction

TABLE S5. OVERALL CLINICAL OUTCOMES AT THE TIME OF PRIMARY ENDPOINT ASSESSMENT

	Total nr of Trials N = 158			Total nr of Patients N = 108839	
	Nr of contributing trials (%)	Rate per 100 person years (IQR)	Range	Nr of contributing patients	Nr of events (%)
Time of primary endpoint assessment (months)	65 (41.14)	12 (9-12)	1-36		
All cause death	106 (67.09)	1.80 (0.97-2.83)	0-12.86	91145	2208 (2.4%)
Cardiac death	98 (62.03)	1.04 (0.49-1.93)	0-8.31	90942	1372 (1.5%)
Myocardial Infarction	110 (69.62)	3.24 (1.45-4.92)	0-23.30	90745	4037 (4.4%)
Target-lesion revascularization	108 (68.35)	5.42 (2.73-12.13)	0-32.14	87559	4237 (4.8%)
Definite stent thrombosis	94 (59.49)	0.63 (0.25-1.15)	0-6.00	84769	693 (0.8%)

Data reported as number of trials (% total nr of trials), medians (25%-75% interquartile ranges [IQR]) and range; number of contributing patients (% total number of patients), and total number of events reported (% of nr of contributing patients).

TABLE S6. OVERALL ANGIOGRAPHIC OUTCOMES

	Total nr of Arms / Trials n=333 / N = 158			
	Nr of contributing Arms/Trials	Median (IQR)	Range	Nr of contributing patients
N of arms / trials reporting any angiographic endpoint	254/122			
Time of angiographic endpoint assessment (months)	252/121	8 (6-9)	3-18	40440
In-stent minimal lumen diameter (mm)	198/ 95	2.25 (2.00-2.42)	1.01 to 2.98	34684
In-stent late lumen loss (mm)	228/109	0.33 (0.16-0.59)	-0.22 to 1.57	37562
In-segment binary restenosis (%)	233/112	10.10 (5.80-16.90)	0.00 to 67.70	39624
In-segment percentual diameter stenosis (%)	209/100	27.00 (21.81-32.90)	2.11 to 66.50	35116

Angiographic endpoints: Data reported as medians (25%-75% interquartile ranges) and range per arm; number of contributing patients (% total number of patients).

¶In 4 trials (9 arms) the sample size of patients for the Angiographic endpoints could not be extracted and the number of randomized patients were used as an approximation of the true sample size.

TABLE S7. CLINICAL OUTCOMES BY STENT SUBGROUP

	Nr of contributing arms (% of subgroup arms)	Rate per 100 person years (IQR)	Range	Nr of contributing patients (% of subgroup)	Nr of events (%)
BMS (any) n = 63 arms / N = 61 trials				n = 13251	
Time of primary endpoint assessment in months*	29 (46.03)	12 (9-12)	1-24		
All-cause Death (% per 100 person years)	39 (61.90)	2.24 (0.00-3.95)	0-13.64	9989 (75.4%)	287 (1.3%)
Cardiac Death (% per 100 person years)	35 (55.56)	1.46 (0.47-4.29)	0-8.57	9558 (72.1%)	221 (1.0%)
Myocardial Infarction (% per 100 person years)	45 (71.43)	4.41 (1.88-6.00)	0-28.00	10965 (82.7%)	408 (1.7%)
Target Lesion Revascularisation (% per 100 person years)	37 (58.73)	15.79 (11.25-25.93)	0-55.71	8519 (64.3%)	975 (5.3%)
Definite Stent Thrombosis (% per 100 person years)	39 (61.90)	0.72 (0.00-2.06)	0-12.00	9597 (72.4%)	132 (0.6%)
DES (any) n = 270 arms / N = 156 trials				n = 97688	
Time of primary endpoint assessment in months*	110 (40.74)	12 (9-12)	1-36		
All-cause Death (% per 100 person years)	184 (68.15)	1.66 (0.87-2.76)	0-12.07	83706 (85.7%)	1997 (1.2%)
Cardiac Death (% per 100 person years)	171 (63.33)	1.00 (0.49-1.97)	0-10.26	83552 (85.5%)	1187 (0.7%)
Myocardial Infarction (% per 100 person years)	205 (75.93)	2.88 (1.25-4.62)	0-36.36	87759 (89.8%)	3867 (2.2%)
Target Lesion Revascularisation (% per 100 person years)	183 (67.78)	4.07 (2.01-7.54)	0-26.67	80098 (82.0%)	3371 (2.1%)
Definite Stent Thrombosis (% per 100 person years)	158 (58.52)	0.50 (0.00-0.96)	0-4.80	77503 (79.3%)	570 (0.4%)
Early DES (Cypher, Taxus, Taxus Element, Endeavor) n = 177 arms / N = 129 trials				n = 57737	
Time of primary endpoint assessment in months*	70 (39.55)	12 (9-12)	1-36		
All-cause Death (% per 100 person years)	116 (65.54)	1.72 (0.87-2.86)	0-12.07	47718 (82.6%)	1161 (1.1%)
Cardiac Death (% per 100 person years)	109 (61.58)	1.03 (0.50-2.11)	0-10.26	48107 (83.3%)	703 (0.7%)
Myocardial Infarction (% per 100 person years)	133 (75.14)	3.01 (1.18-4.72)	0-18.87	50657 (87.7%)	2568 (2.4%)
Target Lesion Revascularisation (% per 100 person years)	117 (66.10)	4.71 (2.46-7.64)	0-18.00	44552 (77.2%)	1926 (2.1%)
Definite Stent Thrombosis (% per 100 person years)	97 (54.80)	0.67 (0.00-1.13)	0-4.80	42536 (73.7%)	389 (0.4%)
New DES n = 67 arms / N = 55 trials				n = 35692	
Time of primary endpoint assessment in months*	31 (46.27)	12 (12-12)	1-24		
All-cause Death (% per 100 person years)	53 (79.10)	1.98 (1.10-2.75)	0-8.52	33633 (94.2%)	802 (1.3%)
Cardiac Death (% per 100 person years)	49 (73.13)	0.94 (0.68-1.55)	0-4.57	32443 (90.9%)	432 (0.7%)
Myocardial Infarction (% per 100 person years)	56 (83.58)	2.81 (1.42-4.59)	0-13.59	33711 (94.4%)	1202 (1.9%)
Target Lesion Revascularisation (% per 100 person years)	52 (77.61)	2.82 (1.59-5.85)	0-13.71	32341 (90.6%)	1243 (2.1%)
Definite Stent Thrombosis (% per 100 person years)	50 (74.63)	0.27 (0.00-0.61)	0-2.50	32433 (90.9%)	155 (0.3%)
FDA approved New DES n = 48 arms / N = 43 trials				n = 24577	
Time of primary endpoint assessment in months*	23 (47.92)	12 (12-12)	1-24		
All-cause Death (% per 100 person years)	37 (77.08)	1.88 (1.01-2.64)	0-8.52	22659 (92.2%)	513 (1.1%)
Cardiac Death (% per 100 person years)	37 (77.08)	0.94 (0.41-1.23)	0-3.26	22162 (90.2%)	270 (0.6%)

Myocardial Infarction (% per 100 person years)	40 (83.33)	2.64 (1.15-4.13)	0-13.59	22862 (93.0%)	843 (1.9%)
Target Lesion Revascularisation (% per 100 person years)	36 (75.00)	2.59 (1.64-4.39)	0-11.11	21600 (87.9%)	701 (1.7%)
Definite Stent Thrombosis (% per 100 person years)	34 (70.83)	0.26 (0.00-0.45)	0-2.20	21584 (87.8%)	84 (0.2%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

*Months

TABLE S8. ANGIOGRAPHIC OUTCOMES BY STENT GROUP

	Nr of contributing Arms/Trials	Median (IQR)	Range	Nr of contributing patients (% of subgroup)
BMS (any) n = 63 arms / N = 61 trials				n = 13251
N of arms/trials reporting any angiographic endpoint	49/ 47			
Time of angiographic endpoint assessment (months)	49/ 47	8 (6-9)	6-13	6183 (46.7%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	34/ 34	1.67 (1.48-1.90)	1.01 to 2.52	4719 (35.6%)
In-stent Late Lumen Loss (mean mm)	43/ 42	0.90 (0.70-1.01)	0.40 to 1.57	5659 (42.7%)
In-segment Binary Restenosis (%)	45/ 44	31.90 (21.30-37.80)	7.70 to 67.70	6041 (45.6%)
In-segment Percentual Diameter Stenosis (mean %)	37/ 37	40.90 (36.80-44.40)	21.81 to 66.50	5403 (40.8%)
DES (any) n = 270 arms / N = 156 trials				n = 97688
N of arms/trials reporting any angiographic endpoint	205/120			
Time of angiographic endpoint assessment (months)	203/119	8 (6-9)	3-18	34257 (35.1%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	164/ 95	2.29 (2.13-2.44)	1.71 to 2.98	29965 (30.7%)
In-stent Late Lumen Loss (mean mm)	185/108	0.25 (0.14-0.44)	-0.22 to 1.05	31903 (32.7%)
In-segment Binary Restenosis (%)	188/111	8.55 (4.65-12.65)	0.00 to 22.20	33583 (34.4%)
In-segment Percentual Diameter Stenosis (mean %)	172/100	24.71 (20.90-30.45)	2.11 to 42.00	29713 (30.4%)
Early DES (Cypher, Taxus, Taxus Element, Endeavor) n = 177 arms / N = 129 trials				n = 57737
N of arms/trials reporting any angiographic endpoint	137/103			
Time of angiographic endpoint assessment (months)	135/102	8 (7-9)	3-18	20992 (36.4%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	110/ 83	2.27 (2.13-2.44)	1.71 to 2.98	18121 (31.4%)
In-stent Late Lumen Loss (mean mm)	123/ 94	0.30 (0.16-0.45)	-0.22 to 0.74	19467 (33.7%)
In-segment Binary Restenosis (%)	127/ 94	9.30 (5.50-12.80)	0.00 to 21.70	20859 (36.1%)
In-segment Percentual Diameter Stenosis (mean %)	120/ 88	25.37 (20.70-30.45)	2.11 to 37.60	19969 (34.6%)
New DES n = 67 arms / N = 55 trials				n = 35692
N of arms/trials reporting any angiographic endpoint	44/ 37			
Time of angiographic endpoint assessment (months)	44/ 37	8 (7-9)	3-18	10257 (28.7%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	37/ 31	2.34 (2.23-2.48)	1.80 to 2.92	9429 (26.4%)
In-stent Late Lumen Loss (mean mm)	40/ 34	0.18 (0.13-0.25)	0.05 to 0.63	9698 (27.2%)
In-segment Binary Restenosis (%)	41/ 34	6.70 (3.90-11.00)	0.00 to 21.50	9874 (27.7%)
In-segment Percentual Diameter Stenosis (mean %)	36/ 31	23.15 (21.36-28.15)	7.20 to 42.00	7355 (20.6%)
FDA approved New DES n = 48 arms / N = 43 trials				n = 24577
N of arms/trials reporting any angiographic endpoint	29/ 27			
Time of angiographic endpoint assessment (months)	29/ 27	8 (7-9)	6-18	5610 (22.8%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	23/ 22	2.39 (2.28-2.51)	2.00 to 2.92	4794 (19.5%)

In-stent Late Lumen Loss (mean mm)	25/ 24	0.16 (0.13-0.22)	0.05 to 0.30	5051 (20.6%)
In-segment Binary Restenosis (%)	26/ 24	5.25 (3.90-8.70)	0.00 to 21.50	5227 (21.3%)
In-segment Percentual Diameter Stenosis (mean %)	23/ 22	22.75 (18.80-24.10)	7.20 to 37.90	4256 (17.3%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

TABLE S9. DES CLINICAL OUTCOMES BY PATIENT AND LESION SUBGROUPS

	Nr of contributing Arms/Trials	Rate per 100 person years	Range	Nr of contributing patients (% of subgroup)	Nr of events (%)
All comers trials	n=40/N=19			n = 40052	
Time of primary endpoint assessment in months*	29/ 15	12 (9-12)	8-36		
All-cause Death (% per 100 person years)	33/ 17	2.05 (1.42-2.75)	0-4.62	35935 (89.7%)	1013 (2.8%)
Cardiac Death (% per 100 person years)	33/ 17	1.11 (0.80-1.38)	0-3.29	36533 (91.2%)	590 (1.6%)
Myocardial Infarction (% per 100 person years)	33/ 17	3.28 (1.74-4.72)	0-13.59	35935 (89.7%)	2218 (6.2%)
Target Lesion Revascularisation (% per 100 person years)	33/ 17	2.91 (1.88-5.74)	1-14.25	34421 (85.9%)	1360 (4.0%)
Definite Stent Thrombosis (% per 100 person years)	31/ 16	0.39 (0.20-0.87)	0-2.67	35323 (88.2%)	247 (0.7%)
STEMI trials	n=28/N=19			n = 12334	
Time of primary endpoint assessment in months*	19/ 12	12 (12-12)	6-12		
All-cause Death (% per 100 person years)	14/ 11	3.46 (3.13-4.52)	2-12.07	9742 (79.0%)	210 (2.2%)
Cardiac Death (% per 100 person years)	18/ 13	3.60 (2.46-4.55)	1-9.68	10523 (85.3%)	201 (1.9%)
Myocardial Infarction (% per 100 person years)	19/ 14	1.95 (1.33-3.33)	0-10.34	10536 (85.4%)	163 (1.5%)
Target Lesion Revascularisation (% per 100 person years)	16/ 11	3.00 (1.76-5.50)	0-8.62	9235 (74.9%)	198 (2.1%)
Definite Stent Thrombosis (% per 100 person years)	15/ 12	0.97 (0.87-2.57)	0-4.29	10086 (81.8%)	104 (1.0%)
Diabetes trials	n=28/N=16			n = 3380	
Time of primary endpoint assessment in months*	5/ 2	36 (36-36)	36-36		
All-cause Death (% per 100 person years)	18/ 9	2.08 (1.33-3.95)	0-6.86	2176 (64.4%)	50 (2.3%)
Cardiac Death (% per 100 person years)	16/ 8	1.50 (0.23-2.37)	0-4.57	1838 (54.4%)	22 (1.2%)
Myocardial Infarction (% per 100 person years)	22/ 11	1.48 (0.67-3.26)	0-8.65	2514 (74.4%)	52 (2.1%)
Target Lesion Revascularisation (% per 100 person years)	22/ 11	5.46 (1.82-9.87)	0-17.53	2514 (74.4%)	154 (6.1%)
Definite Stent Thrombosis (% per 100 person years)	14/ 7	0.20 (0.00-1.19)	0-3.90	1669 (49.4%)	11 (0.7%)
Elderlies trials (mean age≥75 years)	n=1/N=1			n = 800	
Time of primary endpoint assessment in months*	1/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	1/ 1	8.52 (8.52-8.52)	9-8.52	800 (100.0%)	34 (4.3%)
Cardiac Death (% per 100 person years)	1/ 1	3.26 (3.26-3.26)	3-3.26	800 (100.0%)	13 (1.6%)
Myocardial Infarction (% per 100 person years)	1/ 1	4.26 (4.26-4.26)	4-4.26	800 (100.0%)	17 (2.1%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	0.50 (0.50-0.50)	1-0.50	800 (100.0%)	2 (0.3%)
Multivessel disease trials	n=5/N=3			n = 1226	
Time of primary endpoint assessment in months*	1/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	4/ 2	1.16 (1.05-1.24)	1-1.26	616 (50.2%)	10 (1.6%)
Cardiac Death (% per 100 person years)	5/ 3	1.01 (0.94-1.10)	1-4.95	1226 (100.0%)	22 (1.8%)

Myocardial Infarction (% per 100 person years)	5/ 3	1.01 (0.94-3.30)	1-3.96	1226 (100.0%)	21 (1.7%)
Target Lesion Revascularisation (% per 100 person years)	5/ 3	6.06 (3.45-6.27)	3-7.69	1226 (100.0%)	52 (4.2%)
Definite Stent Thrombosis (% per 100 person years)	4/ 2	0.30 (0.00-0.78)	0-0.94	616 (50.2%)	5 (0.8%)
Left-main disease trials	n=5/N=3			n = 1360	
Time of primary endpoint assessment in months*	4/ 2	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	5/ 3	5.52 (4.97-5.56)	4-6.56	1360 (100.0%)	72 (5.3%)
Cardiac Death (% per 100 person years)	1/ 1	3.77 (3.77-3.77)	4-3.77	103 (7.6%)	1 (1.0%)
Myocardial Infarction (% per 100 person years)	5/ 3	4.59 (2.78-4.97)	1-18.87	1360 (100.0%)	47 (3.5%)
Target Lesion Revascularisation (% per 100 person years)	5/ 3	7.54 (6.29-8.90)	4-11.11	1360 (100.0%)	108 (7.9%)
Definite Stent Thrombosis (% per 100 person years)	3/ 2	0.61 (0.00-0.62)	0-0.62	753 (55.4%)	4 (0.5%)
Saphenuous vein graft lesions trials	n=5/N=4			n = 816	
Time of primary endpoint assessment in months*	1/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	3/ 2	5.26 (0.00-10.26)	0-10.26	126 (15.4%)	3 (2.4%)
Cardiac Death (% per 100 person years)	3/ 2	4.95 (0.00-10.26)	0-10.26	661 (81.0%)	17 (2.6%)
Myocardial Infarction (% per 100 person years)	4/ 3	1.98 (0.00-9.87)	0-15.79	736 (90.2%)	15 (2.0%)
Target Lesion Revascularisation (% per 100 person years)	4/ 3	8.40 (5.70-18.60)	5-26.67	736 (90.2%)	27 (3.7%)
Definite Stent Thrombosis (% per 100 person years)	3/ 2	0.00 (0.00-0.00)	0-0.00	126 (15.4%)	0 (0.0%)
In-stent restenose lesions trials	n=6/N=3			n = 716	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Bifurcation lesions trials	n=9/N=5			n = 1508	
Time of primary endpoint assessment in months*	5/ 3	12 (12-12)	9-12		
All-cause Death (% per 100 person years)	7/ 4	0.77 (0.53-1.47)	0-2.76	1358 (90.1%)	15 (1.1%)
Cardiac Death (% per 100 person years)	8/ 4	0.72 (0.49-0.89)	0-1.38	1448 (96.0%)	10 (0.7%)
Myocardial Infarction (% per 100 person years)	9/ 5	1.35 (0.98-1.78)	1-8.89	1508 (100.0%)	25 (1.7%)
Target Lesion Revascularisation (% per 100 person years)	7/ 4	2.76 (1.94-6.37)	1-17.78	1358 (90.1%)	43 (3.2%)
Definite Stent Thrombosis (% per 100 person years)	5/ 3	0.00 (0.00-0.00)	0-4.44	503 (33.4%)	1 (0.2%)
Chronic total occlusion lesions trials	n=9/N=6			n = 911	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	6/ 4	0.00 (0.00-1.92)	0-1.96	599 (65.8%)	3 (0.5%)
Cardiac Death (% per 100 person years)	4/ 2	0.00 (0.00-0.98)	0-1.96	304 (33.4%)	1 (0.3%)
Myocardial Infarction (% per 100 person years)	6/ 4	1.45 (0.00-4.00)	0-4.35	599 (65.8%)	7 (1.2%)
Target Lesion Revascularisation (% per 100 person years)	5/ 3	8.00 (5.83-9.80)	4-15.22	504 (55.3%)	26 (5.2%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	4.00 (4.00-4.00)	4-4.00	200 (22.0%)	2 (1.0%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

*months

TABLE S10. DES ANGIOGRAPHIC OUTCOMES BY PATIENT AND LESION SUBGROUP

	Nr of contributing Arms/Trials	Median (IQR)	Range	Nr of contributing patients (%)
All comers trials	n=40/N=19			n = 40052
N of arms/trials reporting any angiographic endpoint	17/ 8			
Time of angiographic endpoint assessment (months)	17/ 8	8 (8-9)	6-13	5769 (14.4%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	15/ 7	2.30 (2.11-2.42)	2.00 to 2.53	5108 (12.8%)
In-stent Late Lumen Loss (mean mm)	15/ 7	0.19 (0.14-0.25)	0.12 to 0.33	5108 (12.8%)
In-segment Binary Restenosis (%)	17/ 8	7.10 (5.80-10.80)	3.50 to 13.40	5769 (14.4%)
In-segment Percentual Diameter Stenosis (mean %)	17/ 8	24.00 (21.99-27.10)	8.40 to 32.10	5769 (14.4%)
STEMI trials	n=28/N=19			n = 12334
N of arms/trials reporting any angiographic endpoint	18/ 11			
Time of angiographic endpoint assessment (months)	18/ 11	9 (8-9)	6-13	2912 (23.6%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	14/ 9	2.35 (2.11-2.44)	1.84 to 2.80	2410 (19.5%)
In-stent Late Lumen Loss (mean mm)	17/ 10	0.25 (0.10-0.49)	-0.22 to 0.73	2758 (22.4%)
In-segment Binary Restenosis (%)	18/ 11	8.15 (4.30-12.50)	1.70 to 15.90	2912 (23.6%)
In-segment Percentual Diameter Stenosis (mean %)	17/ 10	21.10 (15.00-28.90)	2.11 to 37.60	2873 (23.3%)
Diabetes trials	n=28/N=16			n = 3380
N of arms/trials reporting any angiographic endpoint	23/ 14			
Time of angiographic endpoint assessment (months)	23/ 14	8 (7-9)	6-10	2223 (65.8%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	19/ 11	2.29 (2.10-2.44)	1.80 to 2.57	1800 (53.3%)
In-stent Late Lumen Loss (mean mm)	23/ 14	0.22 (0.14-0.44)	0.09 to 0.74	2223 (65.8%)
In-segment Binary Restenosis (%)	21/ 13	6.90 (4.00-12.80)	0.90 to 20.80	1914 (56.6%)
In-segment Percentual Diameter Stenosis (mean %)	20/ 11	23.21 (20.80-30.05)	16.10 to 42.00	2058 (60.9%)
Elderlies trials (mean age≥75 years)	n=1/N=1			n = 800
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (0.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Multivessel disease trials	n=5/N=3			n = 1226
N of arms/trials reporting any angiographic endpoint	5/ 3			
Time of angiographic endpoint assessment (months)	5/ 3	8 (8-9)	7-9	607 (49.5%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	4/ 2	2.61 (2.23-2.92)	2.17 to 2.93	383 (31.2%)
In-stent Late Lumen Loss (mean mm)	4/ 2	0.11 (0.07-0.19)	0.05 to 0.24	383 (31.2%)

In-segment Binary Restenosis (%)	3/ 2	9.60 (7.10-15.00)	7.10 to 15.00	440 (35.9%)
In-segment Percentual Diameter Stenosis (mean %)	4/ 2	17.30 (11.71-24.59)	11.11 to 26.87	383 (31.2%)
Left-main disease trials	n=5/N=3			n = 1360
N of arms/trials reporting any angiographic endpoint	5/ 3			
Time of angiographic endpoint assessment (months)	5/ 3	6 (6-7)	6-7	1043 (76.7%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.74 (2.74-2.74)	2.74 to 2.74	50 (3.7%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.22 (0.22-0.22)	0.22 to 0.22	50 (3.7%)
In-segment Binary Restenosis (%)	5/ 3	16.80 (16.00-19.40)	6.00 to 21.50	1043 (76.7%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	15.80 (15.80-15.80)	15.80 to 15.80	50 (3.7%)
Saphenuous vein graft lesions trials	n=5/N=4			n = 816
N of arms/trials reporting any angiographic endpoint	5/ 4			
Time of angiographic endpoint assessment (months)	5/ 4	9 (7-9)	6-12	333 (40.8%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	4/ 3	2.40 (2.28-2.50)	2.25 to 2.50	109 (13.4%)
In-stent Late Lumen Loss (mean mm)	4/ 3	0.40 (0.34-0.51)	0.30 to 0.59	109 (13.4%)
In-segment Binary Restenosis (%)	3/ 3	13.60 (9.00-15.00)	9.00 to 15.00	292 (35.8%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 2	26.50 (25.00-28.00)	25.00 to 28.00	68 (8.3%)
In-stent restenose lesions trials	n=6/N=3			n = 716
N of arms/trials reporting any angiographic endpoint	6/ 3			
Time of angiographic endpoint assessment (months)	4/ 2	8 (7-9)	7-9	224 (31.3%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 1	2.15 (2.14-2.16)	2.14 to 2.16	381 (53.2%)
In-stent Late Lumen Loss (mean mm)	2/ 1	0.39 (0.38-0.40)	0.38 to 0.40	381 (53.2%)
In-segment Binary Restenosis (%)	6/ 3	16.65 (14.30-20.60)	5.00 to 21.70	605 (84.5%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 1	33.65 (33.30-34.00)	33.30 to 34.00	381 (53.2%)
Bifurcation lesions trials	n=9/N=5			n = 1508
N of arms/trials reporting any angiographic endpoint	5/ 3			
Time of angiographic endpoint assessment (months)	7/ 4	9 (8-18)	8-18	882 (58.5%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 1	2.33 (2.20-2.45)	2.20 to 2.45	593 (39.3%)
In-stent Late Lumen Loss (mean mm)	3/ 2	0.37 (0.27-0.57)	0.27 to 0.57	623 (41.3%)
In-segment Binary Restenosis (%)	2/ 1	8.85 (5.50-12.20)	5.50 to 12.20	593 (39.3%)
In-segment Percentual Diameter Stenosis (mean %)	4/ 2	24.55 (20.80-28.25)	20.00 to 29.00	702 (46.6%)
Chronic total occlusion lesions trials	n=9/N=6			n = 911
N of arms/trials reporting any angiographic endpoint	9/ 6			
Time of angiographic endpoint assessment (months)	9/ 6	8 (8-8)	6-9	585 (64.2%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	5/ 3	2.36 (2.26-2.39)	1.89 to 2.41	301 (33.0%)
In-stent Late Lumen Loss (mean mm)	6/ 4	0.05 (0.03-0.20)	-0.13 to 0.54	395 (43.4%)
In-segment Binary Restenosis (%)	9/ 6	11.00 (7.10-13.70)	5.30 to 17.40	585 (64.2%)
In-segment Percentual Diameter Stenosis (mean %)	9/ 6	31.10 (30.60-32.19)	24.90 to 33.37	585 (64.2%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

TABLE S11. BMS CLINICAL OUTCOMES BY PATIENT AND LESION SUBGROUP

	Nr of contributing Arms/Trials	Rate per 100 person years	Range	Nr of contributing patients (% of subgroup)	Nr of events (%)
All comers trials	n=2/N=2			n = 4327	
Time of primary endpoint assessment in months*	1/ 1	24 (24-24)	24-24		
All-cause Death (% per 100 person years)	1/ 1	2.22 (2.22-2.22)	2-2.22	2314 (53.5%)	34 (1.5%)
Cardiac Death (% per 100 person years)	1/ 1	1.44 (1.44-1.44)	1-1.44	2314 (53.5%)	22 (1.0%)
Myocardial Infarction (% per 100 person years)	1/ 1	1.31 (1.31-1.31)	1-1.31	2314 (53.5%)	20 (0.9%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Target Vessel Revascularisation (% per 100 person years)	1/ 1	0.39 (0.39-0.39)	0-0.39	2314 (53.5%)	6 (0.3%)
Definite Stent Thrombosis (% per 100 person years)					
Definite or Probable Stent Thrombosis (% per 100 person years)	n=15/N=14			n = 9793	
STEMI trials	9/ 9	3.95 (3.48-6.47)	2-13.64	8823 (90.1%)	139 (1.6%)
Time of primary endpoint assessment in months*	12/ 11	4.93 (2.74-7.47)	2-8.57	8829 (90.2%)	121 (1.4%)
All-cause Death (% per 100 person years)	11/ 11	3.83 (1.94-6.67)	1-13.64	8742 (89.3%)	119 (1.4%)
Cardiac Death (% per 100 person years)	10/ 9	11.22 (7.21-28.00)	5-55.71	7541 (77.0%)	240 (3.2%)
Myocardial Infarction (% per 100 person years)	12/ 11	1.97 (1.04-3.94)	0-12.00	9003 (91.9%)	86 (1.0%)
Target Lesion Revascularisation (% per 100 person years)					
Target Vessel Revascularisation (% per 100 person years)	n=5/N=5			n = 766	
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-		
Definite or Probable Stent Thrombosis (% per 100 person years)	1/ 1	4.17 (4.17-4.17)	4-4.17	200 (26.1%)	4 (2.0%)
Diabetes trials	1/ 1	5.21 (5.21-5.21)	5-5.21	200 (26.1%)	5 (2.5%)
Time of primary endpoint assessment in months*	1/ 1	25.00 (25.00-25.00)	25-25.00	200 (26.1%)	24 (12.0%)
All-cause Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)					
Myocardial Infarction (% per 100 person years)	n=1/N=1			n = 800	
Target Lesion Revascularisation (% per 100 person years)	1/ 1	12 (12-12)	12-12		
Target Vessel Revascularisation (% per 100 person years)	1/ 1	7.23 (7.23-7.23)	7-7.23	800 (100.0%)	29 (3.6%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	4.74 (4.74-4.74)	5-4.74	800 (100.0%)	19 (2.4%)
Definite or Probable Stent Thrombosis (% per 100 person years)	1/ 1	8.73 (8.73-8.73)	9-8.73	800 (100.0%)	35 (4.4%)
Elderlies trials (mean age≥75 years)	1/ 1	0.00 (0.00-0.00)	0-0.00	800 (100.0%)	0 (0.0%)
Time of primary endpoint assessment in months*					
All-cause Death (% per 100 person years)	n=1/N=1			n = 610	
Cardiac Death (% per 100 person years)	1/ 1	12 (12-12)	12-12		
Myocardial Infarction (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)

Target Lesion Revascularisation (% per 100 person years)	1/ 1	4.56 (4.56-4.56)	5-4.56	610 (100.0%)	14 (2.3%)
Target Vessel Revascularisation (% per 100 person years)	1/ 1	5.86 (5.86-5.86)	6-5.86	610 (100.0%)	18 (3.0%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	12.05 (12.05-12.05)	12-12.05	610 (100.0%)	37 (6.1%)
Definite or Probable Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Multivessel disease trials	n=1/N=1			n = 103	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	1/ 1	4.00 (4.00-4.00)	4-4.00	103 (100.0%)	1 (1.0%)
Cardiac Death (% per 100 person years)	1/ 1	0.00 (0.00-0.00)	0-0.00	103 (100.0%)	0 (0.0%)
Myocardial Infarction (% per 100 person years)	1/ 1	28.00 (28.00-28.00)	28-28.00	103 (100.0%)	7 (6.8%)
Target Lesion Revascularisation (% per 100 person years)	1/ 1	32.00 (32.00-32.00)	32-32.00	103 (100.0%)	8 (7.8%)
Target Vessel Revascularisation (% per 100 person years)	1/ 1	0.00 (0.00-0.00)	0-0.00	103 (100.0%)	0 (0.0%)
Definite Stent Thrombosis (% per 100 person years)					
Definite or Probable Stent Thrombosis (% per 100 person years)	n=3/N=3			n = 765	
Left-main disease trials	1/ 1	0.00 (0.00-0.00)	0-0.00	75 (9.8%)	0 (0.0%)
Time of primary endpoint assessment in months*	2/ 2	2.28 (0.00-4.56)	0-4.56	685 (89.5%)	14 (2.0%)
All-cause Death (% per 100 person years)	2/ 2	5.63 (5.41-5.86)	5-5.86	685 (89.5%)	19 (2.8%)
Cardiac Death (% per 100 person years)	2/ 2	27.65 (12.05-43.24)	12-43.24	685 (89.5%)	45 (6.6%)
Myocardial Infarction (% per 100 person years)	1/ 1	0.00 (0.00-0.00)	0-0.00	75 (9.8%)	0 (0.0%)
Target Lesion Revascularisation (% per 100 person years)					
Target Vessel Revascularisation (% per 100 person years)	n=0/N=0			n = 0	
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-		
Definite or Probable Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Saphenuous vein graft lesions trials	0/ 0	(-)	-	0 (.%)	0 (.%)
Time of primary endpoint assessment in months*	0/ 0	(-)	-	0 (.%)	0 (.%)
All-cause Death (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Cardiac Death (% per 100 person years)					
Myocardial Infarction (% per 100 person years)	n=3/N=2			n = 120	
Target Lesion Revascularisation (% per 100 person years)	3/ 2	12 (9-12)	9-12		
Target Vessel Revascularisation (% per 100 person years)	3/ 2	0.00 (0.00-0.00)	0-0.00	120 (100.0%)	0 (0.0%)
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Definite or Probable Stent Thrombosis (% per 100 person years)	3/ 2	0.00 (0.00-4.44)	0-4.44	120 (100.0%)	1 (0.8%)
In-stent restenose lesions trials	3/ 2	0.00 (0.00-0.00)	0-0.00	120 (100.0%)	0 (0.0%)
Time of primary endpoint assessment in months*					
All-cause Death (% per 100 person years)	n=3/N=3			n = 447	
Cardiac Death (% per 100 person years)	0/ 0	(-)	-		
Myocardial Infarction (% per 100 person years)	2/ 2	0.00 (0.00-0.00)	0-0.00	295 (66.0%)	0 (0.0%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Target Vessel Revascularisation (% per 100 person years)	2/ 2	3.00 (0.00-6.00)	0-6.00	295 (66.0%)	3 (1.0%)

Definite Stent Thrombosis (% per 100 person years)	1/ 1	38.00 (38.00-38.00)	38-38.00	200 (44.7%)	19 (9.5%)
Definite or Probable Stent Thrombosis (% per 100 person years)	1/ 1	0.00 (0.00-0.00)	0-0.00	200 (44.7%)	0 (0.0%)
Bifurcation lesions trials	n=3/N=2			n = 120	
Time of primary endpoint assessment in months*	3/ 2	12 (9-12)	9-12		
All-cause Death (% per 100 person years)	3/ 2	0.00 (0.00-0.00)	0-0.00	120 (100.0%)	
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	
Myocardial Infarction (% per 100 person years)	3/ 2	0.00 (0.00-4.44)	0-4.44	120 (100.0%)	
Target Lesion Revascularisation (% per 100 person years)	3/ 2	13.79 (13.33-17.78)	13-17.78	120 (100.0%)	
Target Vessel Revascularisation (% per 100 person years)	3/ 2	0.00 (0.00-17.78)	0-17.78	120 (100.0%)	
Definite Stent Thrombosis (% per 100 person years)	3/ 2	0.00 (0.00-0.00)	0-0.00	120 (100.0%)	
Definite or Probable Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	
Chronic total occlusion lesions trials	n=3/N=3			n = 447	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	2/ 2	0.00 (0.00-0.00)	0-0.00	295 (66.0%)	
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	
Myocardial Infarction (% per 100 person years)	2/ 2	3.00 (0.00-6.00)	0-6.00	295 (66.0%)	
Target Lesion Revascularisation (% per 100 person years)	1/ 1	38.00 (38.00-38.00)	38-38.00	200 (44.7%)	
Target Vessel Revascularisation (% per 100 person years)	2/ 2	75.33 (44.00-106.67)	44-106.67	295 (66.0%)	
Definite Stent Thrombosis (% per 100 person years)	1/ 1	0.00 (0.00-0.00)	0-0.00	200 (44.7%)	
Definite or Probable Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

*months

TABLE S12. BMS ANGIOGRAPHIC OUTCOMES BY PATIENT AND LESION SUBGROUP

	Nr of contributing Arms/Trials	Median (IQR)	Range	Nr of contributing patients (% of subgroup)
All comers trials	n=2/N=2			n = 4327
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (0.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
STEMI trials	n=15/N=14			n = 9793
N of arms/trials reporting any angiographic endpoint	8/ 7			
Time of angiographic endpoint assessment (months)	8/ 7	8 (6-10)	6-13	1820 (18.6%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	5/ 5	1.98 (1.90-2.00)	1.48 to 2.25	1584 (16.2%)
In-stent Late Lumen Loss (mean mm)	5/ 5	0.70 (0.69-0.82)	0.60 to 1.01	1584 (16.2%)
In-segment Binary Restenosis (%)	8/ 7	20.60 (14.95-33.00)	11.30 to 37.80	1820 (18.6%)
In-segment Percentual Diameter Stenosis (mean %)	5/ 5	37.00 (36.80-37.40)	34.60 to 42.00	1692 (17.3%)
Diabetes trials	n=5/N=5			n = 766
N of arms/trials reporting any angiographic endpoint	5/ 5			
Time of angiographic endpoint assessment (months)	5/ 5	8 (8-9)	6-9	268 (35.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	3/ 3	1.46 (1.28-1.48)	1.28 to 1.48	158 (20.6%)
In-stent Late Lumen Loss (mean mm)	5/ 5	0.96 (0.76-0.99)	0.67 to 1.10	268 (35.0%)
In-segment Binary Restenosis (%)	5/ 5	38.80 (36.70-42.10)	33.70 to 57.10	268 (35.0%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 2	47.22 (46.00-48.43)	46.00 to 48.43	132 (17.2%)
Elderlies trials (mean age≥75 years)	n=1/N=1			n = 800
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (0.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Multivessel disease trials	n=1/N=1			n = 610
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	7 (7-7)	7-7	214 (35.1%)

in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	1/ 1	29.00 (29.00-29.00)	29.00 to 29.00	214 (35.1%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Left-main disease trials	n=1/N=1			n = 103
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	6 (6-6)	6-6	53 (51.5%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.52 (2.52-2.52)	2.52 to 2.52	53 (51.5%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.60 (0.60-0.60)	0.60 to 0.60	53 (51.5%)
In-segment Binary Restenosis (%)	1/ 1	22.00 (22.00-22.00)	22.00 to 22.00	53 (51.5%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	21.81 (21.81-21.81)	21.81 to 21.81	53 (51.5%)
Saphenuous vein graft lesions trials	n=3/N=3			n = 765
N of arms/trials reporting any angiographic endpoint	3/ 3			
Time of angiographic endpoint assessment (months)	3/ 3	7 (6-12)	6-12	284 (37.1%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 2	1.68 (1.39-1.97)	1.39 to 1.97	70 (9.2%)
In-stent Late Lumen Loss (mean mm)	2/ 2	1.04 (0.79-1.29)	0.79 to 1.29	70 (9.2%)
In-segment Binary Restenosis (%)	3/ 3	32.60 (29.00-51.00)	29.00 to 51.00	284 (37.1%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 2	46.00 (39.00-53.00)	39.00 to 53.00	70 (9.2%)
In-stent restenose lesions trials	n=0/N=0			n = 0
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (.%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (.%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (.%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (.%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (.%)
Bifurcation lesions trials	n=3/N=2			n = 120
N of arms/trials reporting any angiographic endpoint	3/ 2			
Time of angiographic endpoint assessment (months)	3/ 2	12 (9-12)	9-12	89 (74.2%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	3/ 2	0.61 (0.40-0.64)	0.40 to 0.64	89 (74.2%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Chronic total occlusion lesions trials	n=3/N=3			n = 447
N of arms/trials reporting any angiographic endpoint	3/ 3			
Time of angiographic endpoint assessment (months)	3/ 3	6 (6-8)	6-8	205 (45.9%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	1.01 (1.01-1.01)	1.01 to 1.01	66 (14.8%)
In-stent Late Lumen Loss (mean mm)	2/ 2	1.33 (1.09-1.57)	1.09 to 1.57	160 (35.8%)
In-segment Binary Restenosis (%)	3/ 3	60.00 (41.00-67.70)	41.00 to 67.70	205 (45.9%)

In-segment Percentual Diameter Stenosis (mean %)	3/ 3	66.40 (53.32-66.50)	53.32 to 66.50	205 (45.9%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

TABLE S13. EARLY DES CLINICAL OUTCOMES BY PATIENT AND LESION SUBGROUP

	Nr of contributing Arms/Trials	Rate per 100 person years	Range	Nr of contributing patients (% of subgroup)	Nr of events (%)
All comers trials	n=21/N=15			n = 31518	
Time of primary endpoint assessment in months*	15/ 11	9 (9-24)	8-36		
All-cause Death (% per 100 person years)	16/ 12	1.73 (1.16-2.43)	0-3.76	27401 (86.9%)	588 (2.1%)
Cardiac Death (% per 100 person years)	16/ 12	0.85 (0.74-1.30)	0-3.29	27999 (88.8%)	342 (1.2%)
Myocardial Infarction (% per 100 person years)	16/ 12	3.82 (0.86-4.80)	0-6.12	27401 (86.9%)	1494 (5.5%)
Target Lesion Revascularisation (% per 100 person years)	17/ 12	4.75 (1.90-6.59)	1-14.25	25887 (82.1%)	825 (3.2%)
Definite Stent Thrombosis (% per 100 person years)	15/ 11	0.42 (0.22-1.49)	0-2.67	26789 (85.0%)	160 (0.6%)
STEMI trials	n=25/N=16			n = 9043	
Time of primary endpoint assessment in months*	17/ 10	12 (12-12)	6-12		
All-cause Death (% per 100 person years)	11/ 8	3.46 (2.59-4.52)	2-12.07	6451 (71.3%)	150 (2.3%)
Cardiac Death (% per 100 person years)	15/ 10	3.87 (2.39-4.55)	1-9.68	7232 (80.0%)	148 (2.0%)
Myocardial Infarction (% per 100 person years)	16/ 11	1.96 (1.20-3.46)	0-10.34	7245 (80.1%)	137 (1.9%)
Target Lesion Revascularisation (% per 100 person years)	13/ 8	3.33 (1.95-5.16)	0-8.62	5944 (65.7%)	157 (2.6%)
Definite Stent Thrombosis (% per 100 person years)	13/ 10	1.11 (0.92-2.57)	0-4.29	7421 (82.1%)	95 (1.3%)
Diabetes trials	n=23/N=15			n = 3207	
Time of primary endpoint assessment in months*	5/ 2	36 (36-36)	36-36		
All-cause Death (% per 100 person years)	15/ 9	2.19 (1.33-3.95)	0-6.40	2176 (67.9%)	41 (1.9%)
Cardiac Death (% per 100 person years)	13/ 8	1.82 (0.67-2.35)	0-3.55	1838 (57.3%)	17 (0.9%)
Myocardial Infarction (% per 100 person years)	19/ 11	1.19 (0.44-3.20)	0-8.65	2514 (78.4%)	40 (1.6%)
Target Lesion Revascularisation (% per 100 person years)	19/ 11	4.71 (1.82-9.87)	0-17.53	2514 (78.4%)	119 (4.7%)
Definite Stent Thrombosis (% per 100 person years)	11/ 7	0.67 (0.00-1.82)	0-3.90	1669 (52.0%)	11 (0.7%)
Elderlies trials (mean age≥75 years)	n=0/N=0			n = 0	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Multivessel disease trials	n=3/N=2			n = 616	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	3/ 2	1.22 (1.10-1.26)	1-1.26	616 (100.0%)	9 (1.5%)
Cardiac Death (% per 100 person years)	3/ 2	0.94 (0.61-1.10)	1-1.10	616 (100.0%)	6 (1.0%)

Myocardial Infarction (% per 100 person years)	3/ 2	0.94 (0.61-3.30)	1-3.30	616 (100.0%)	8 (1.3%)
Target Lesion Revascularisation (% per 100 person years)	3/ 2	3.45 (2.74-7.69)	3-7.69	616 (100.0%)	27 (4.4%)
Definite Stent Thrombosis (% per 100 person years)	3/ 2	0.61 (0.00-0.94)	0-0.94	616 (100.0%)	5 (0.8%)
Left-main disease trials	n=3/N=2			n = 710	
Time of primary endpoint assessment in months*	2/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	3/ 2	4.97 (3.77-6.56)	4-6.56	710 (100.0%)	36 (5.1%)
Cardiac Death (% per 100 person years)	1/ 1	3.77 (3.77-3.77)	4-3.77	103 (14.5%)	1 (1.0%)
Myocardial Infarction (% per 100 person years)	3/ 2	4.97 (4.59-18.87)	5-18.87	710 (100.0%)	34 (4.8%)
Target Lesion Revascularisation (% per 100 person years)	3/ 2	6.29 (3.77-7.54)	4-7.54	710 (100.0%)	43 (6.1%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	0.00 (0.00-0.00)	0-0.00	103 (14.5%)	0 (0.0%)
Saphenuous vein graft lesions trials	n=3/N=3			n = 206	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	2/ 2	7.76 (5.26-10.26)	5-10.26	126 (61.2%)	3 (2.4%)
Cardiac Death (% per 100 person years)	1/ 1	10.26 (10.26-10.26)	10-10.26	51 (24.8%)	2 (3.9%)
Myocardial Infarction (% per 100 person years)	2/ 2	7.89 (0.00-15.79)	0-15.79	126 (61.2%)	3 (2.4%)
Target Lesion Revascularisation (% per 100 person years)	2/ 2	7.83 (5.13-10.53)	5-10.53	126 (61.2%)	3 (2.4%)
Definite Stent Thrombosis (% per 100 person years)	2/ 2	0.00 (0.00-0.00)	0-0.00	126 (61.2%)	0 (0.0%)
In-stent restenose lesions trials	n=5/N=3			n = 716	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Bifurcation lesions trials	n=7/N=5			n = 1508	
Time of primary endpoint assessment in months*	4/ 3	12 (11-12)	9-12		
All-cause Death (% per 100 person years)	6/ 4	0.87 (0.53-1.47)	0-2.76	1358 (90.1%)	14 (1.0%)
Cardiac Death (% per 100 person years)	6/ 4	0.63 (0.49-0.89)	0-1.38	1448 (96.0%)	8 (0.6%)
Myocardial Infarction (% per 100 person years)	7/ 5	1.05 (0.97-1.78)	1-8.89	1508 (100.0%)	17 (1.1%)
Target Lesion Revascularisation (% per 100 person years)	6/ 4	2.40 (1.94-6.37)	1-17.78	1358 (90.1%)	38 (2.8%)
Definite Stent Thrombosis (% per 100 person years)	3/ 3	0.00 (0.00-4.44)	0-4.44	503 (33.4%)	1 (0.2%)
Chronic total occlusion lesions trials	n=7/N=5			n = 816	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	4/ 3	0.00 (0.00-0.98)	0-1.96	504 (61.8%)	1 (0.2%)
Cardiac Death (% per 100 person years)	3/ 2	0.00 (0.00-1.96)	0-1.96	304 (37.3%)	1 (0.3%)
Myocardial Infarction (% per 100 person years)	4/ 3	2.49 (0.49-4.17)	0-4.35	504 (61.8%)	5 (1.0%)
Target Lesion Revascularisation (% per 100 person years)	4/ 3	8.90 (6.91-12.51)	6-15.22	504 (61.8%)	22 (4.4%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	4.00 (4.00-4.00)	4-4.00	200 (24.5%)	2 (1.0%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

*months

TABLE S14. EARLY DES ANGIOGRAPHIC OUTCOMES BY PATIENT AND LESION SUBGROUP

	Nr of contributing Arms/Trials	Median (IQR)	Range	Nr of contributing patients (% of subgroup)
All comers trials	n=21/N=15			n = 31518
N of arms/trials reporting any angiographic endpoint	8/ 6			
Time of angiographic endpoint assessment (months)	8/ 6	8 (8-9)	6-9	2465 (7.8%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	6/ 5	2.30 (2.11-2.44)	2.00 to 2.53	1804 (5.7%)
In-stent Late Lumen Loss (mean mm)	6/ 5	0.22 (0.14-0.28)	0.12 to 0.33	1804 (5.7%)
In-segment Binary Restenosis (%)	8/ 6	10.60 (6.20-11.95)	3.50 to 13.40	2465 (7.8%)
In-segment Percentual Diameter Stenosis (mean %)	8/ 6	21.70 (15.20-28.21)	8.40 to 32.10	2465 (7.8%)
STEMI trials	n=25/N=16			n = 9043
N of arms/trials reporting any angiographic endpoint	17/ 10			
Time of angiographic endpoint assessment (months)	17/ 10	9 (8-9)	6-13	2654 (29.3%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	13/ 8	2.34 (2.11-2.42)	1.84 to 2.80	2152 (23.8%)
In-stent Late Lumen Loss (mean mm)	16/ 9	0.31 (0.11-0.51)	-0.22 to 0.73	2500 (27.6%)
In-segment Binary Restenosis (%)	17/ 10	9.60 (4.30-12.50)	1.70 to 15.90	2654 (29.3%)
In-segment Percentual Diameter Stenosis (mean %)	16/ 9	20.85 (14.55-28.75)	2.11 to 37.60	2615 (28.9%)
Diabetes trials	n=23/N=15			n = 3207
N of arms/trials reporting any angiographic endpoint	18/ 13			
Time of angiographic endpoint assessment (months)	18/ 13	8 (6-9)	6-10	1637 (51.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	16/ 11	2.27 (2.13-2.39)	1.96 to 2.48	1471 (45.9%)
In-stent Late Lumen Loss (mean mm)	18/ 13	0.23 (0.19-0.44)	0.09 to 0.74	1637 (51.0%)
In-segment Binary Restenosis (%)	17/ 12	6.90 (6.50-12.80)	2.80 to 20.80	1546 (48.2%)
In-segment Percentual Diameter Stenosis (mean %)	16/ 11	24.50 (20.80-30.05)	16.10 to 37.00	1511 (47.1%)
Elderlies trials (mean age≥75 years)	n=0/N=0			n = 0
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (.%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (.%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (.%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (.%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (.%)
Multivessel disease trials	n=3/N=2			n = 616
N of arms/trials reporting any angiographic endpoint	3/ 2			
Time of angiographic endpoint assessment (months)	3/ 2	8 (8-9)	8-9	293 (47.6%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	3/ 2	2.92 (2.17-2.93)	2.17 to 2.93	293 (47.6%)

In-stent Late Lumen Loss (mean mm)	3/ 2	0.13 (0.09-0.24)	0.09 to 0.24	293 (47.6%)
In-segment Binary Restenosis (%)	2/ 1	8.35 (7.10-9.60)	7.10 to 9.60	216 (35.1%)
In-segment Percentual Diameter Stenosis (mean %)	3/ 2	12.30 (11.11-22.30)	11.11 to 22.30	293 (47.6%)
Left-main disease trials	n=3/N=2			n = 710
N of arms/trials reporting any angiographic endpoint	3/ 2			
Time of angiographic endpoint assessment (months)	3/ 2	6 (6-6)	6-6	580 (81.7%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.74 (2.74-2.74)	2.74 to 2.74	50 (7.0%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.22 (0.22-0.22)	0.22 to 0.22	50 (7.0%)
In-segment Binary Restenosis (%)	3/ 2	16.00 (6.00-19.40)	6.00 to 19.40	580 (81.7%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	15.80 (15.80-15.80)	15.80 to 15.80	50 (7.0%)
Saphenuous vein graft lesions trials	n=3/N=3			n = 206
N of arms/trials reporting any angiographic endpoint	3/ 3			
Time of angiographic endpoint assessment (months)	3/ 3	9 (6-12)	6-12	88 (42.7%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	3/ 3	2.49 (2.31-2.50)	2.31 to 2.50	88 (42.7%)
In-stent Late Lumen Loss (mean mm)	3/ 3	0.38 (0.30-0.42)	0.30 to 0.42	88 (42.7%)
In-segment Binary Restenosis (%)	2/ 2	11.30 (9.00-13.60)	9.00 to 13.60	68 (33.0%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 2	26.50 (25.00-28.00)	25.00 to 28.00	68 (33.0%)
In-stent restenose lesions trials	n=5/N=3			n = 716
N of arms/trials reporting any angiographic endpoint	5/ 3			
Time of angiographic endpoint assessment (months)	3/ 2	7 (7-9)	7-9	203 (28.4%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 1	2.15 (2.14-2.16)	2.14 to 2.16	381 (53.2%)
In-stent Late Lumen Loss (mean mm)	2/ 1	0.39 (0.38-0.40)	0.38 to 0.40	381 (53.2%)
In-segment Binary Restenosis (%)	5/ 3	19.00 (14.30-20.60)	5.00 to 21.70	584 (81.6%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 1	33.65 (33.30-34.00)	33.30 to 34.00	381 (53.2%)
Bifurcation lesions trials	n=7/N=5			n = 1508
N of arms/trials reporting any angiographic endpoint	5/ 3			
Time of angiographic endpoint assessment (months)	6/ 4	9 (8-9)	8-18	807 (53.5%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 1	2.33 (2.20-2.45)	2.20 to 2.45	593 (39.3%)
In-stent Late Lumen Loss (mean mm)	3/ 2	0.37 (0.27-0.57)	0.27 to 0.57	623 (41.3%)
In-segment Binary Restenosis (%)	2/ 1	8.85 (5.50-12.20)	5.50 to 12.20	593 (39.3%)
In-segment Percentual Diameter Stenosis (mean %)	4/ 2	24.55 (20.80-28.25)	20.00 to 29.00	702 (46.6%)
Chronic total occlusion lesions trials	n=7/N=5			n = 816
N of arms/trials reporting any angiographic endpoint	7/ 5			
Time of angiographic endpoint assessment (months)	7/ 5	8 (8-9)	6-9	454 (55.6%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	4/ 3	2.31 (2.08-2.38)	1.89 to 2.41	216 (26.5%)
In-stent Late Lumen Loss (mean mm)	5/ 4	0.05 (0.03-0.20)	-0.13 to 0.54	310 (38.0%)
In-segment Binary Restenosis (%)	7/ 5	11.00 (6.20-13.70)	5.30 to 14.10	454 (55.6%)
In-segment Percentual Diameter Stenosis (mean %)	7/ 5	31.85 (30.60-32.31)	24.90 to 33.37	454 (55.6%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

TABLE S15. NEW DES CLINICAL OUTCOMES BY PATIENT AND LESION SUBGROUP

	Nr of contributing Arms/Trials	Rate per 100 person years	Range	Nr of contributing patients (% of subgroup)	Nr of events (%)
All comers trials	n=22/N=16			n = 38038	
Time of primary endpoint assessment in months*	16/ 13	12 (11-12)	9-36		
All-cause Death (% per 100 person years)	19/ 15	2.47 (1.61-2.87)	1-4.62	34721 (91.3%)	631 (1.8%)
Cardiac Death (% per 100 person years)	19/ 15	1.17 (0.84-1.69)	1-2.69	34721 (91.3%)	369 (1.1%)
Myocardial Infarction (% per 100 person years)	19/ 15	2.94 (1.89-4.08)	0-13.59	34721 (91.3%)	1367 (3.9%)
Target Lesion Revascularisation (% per 100 person years)	18/ 14	2.48 (1.75-3.93)	1-8.39	32407 (85.2%)	834 (2.6%)
Definite Stent Thrombosis (% per 100 person years)	18/ 14	0.35 (0.20-0.72)	0-2.49	34321 (90.2%)	131 (0.4%)
STEMI trials	n=7/N=7			n = 4645	
Time of primary endpoint assessment in months*	5/ 5	12 (12-12)	6-12		
All-cause Death (% per 100 person years)	3/ 3	3.45 (3.13-3.46)	3-3.46	3276 (70.5%)	51 (1.6%)
Cardiac Death (% per 100 person years)	4/ 4	2.99 (2.62-4.27)	2-5.35	4151 (89.4%)	57 (1.4%)
Myocardial Infarction (% per 100 person years)	4/ 4	1.16 (0.94-1.62)	1-1.91	4151 (89.4%)	25 (0.6%)
Target Lesion Revascularisation (% per 100 person years)	4/ 4	2.30 (1.85-2.57)	2-2.67	4151 (89.4%)	36 (0.9%)
Definite Stent Thrombosis (% per 100 person years)	3/ 3	0.87 (0.53-0.89)	1-0.89	3540 (76.2%)	11 (0.3%)
Diabetes trials	n=7/N=7			n = 1646	
Time of primary endpoint assessment in months*	1/ 1	36 (36-36)	36-36		
All-cause Death (% per 100 person years)	5/ 5	1.78 (1.40-3.64)	0-6.86	1173 (71.3%)	15 (1.3%)
Cardiac Death (% per 100 person years)	4/ 4	1.14 (0.23-3.19)	0-4.57	947 (57.5%)	6 (0.6%)
Myocardial Infarction (% per 100 person years)	5/ 5	1.82 (1.78-3.26)	1-4.57	1173 (71.3%)	17 (1.4%)
Target Lesion Revascularisation (% per 100 person years)	5/ 5	6.22 (1.82-9.77)	2-13.71	1173 (71.3%)	50 (4.3%)
Definite Stent Thrombosis (% per 100 person years)	4/ 4	0.00 (0.00-0.91)	0-1.82	947 (57.5%)	1 (0.1%)
Elderlies trials (mean age≥75 years)	n=1/N=1			n = 800	
Time of primary endpoint assessment in months*	1/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	1/ 1	8.52 (8.52-8.52)	9-8.52	800 (100.0%)	34 (4.3%)
Cardiac Death (% per 100 person years)	1/ 1	3.26 (3.26-3.26)	3-3.26	800 (100.0%)	13 (1.6%)
Myocardial Infarction (% per 100 person years)	1/ 1	4.26 (4.26-4.26)	4-4.26	800 (100.0%)	17 (2.1%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	0.50 (0.50-0.50)	1-0.50	800 (100.0%)	2 (0.3%)
Multivessel disease trials	n=1/N=1			n = 200	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	1/ 1	1.01 (1.01-1.01)	1-1.01	200 (100.0%)	1 (0.5%)
Cardiac Death (% per 100 person years)	1/ 1	1.01 (1.01-1.01)	1-1.01	200 (100.0%)	1 (0.5%)

Myocardial Infarction (% per 100 person years)	1/ 1	1.01 (1.01-1.01)	1-1.01	200 (100.0%)	1 (0.5%)
Target Lesion Revascularisation (% per 100 person years)	1/ 1	6.06 (6.06-6.06)	6-6.06	200 (100.0%)	6 (3.0%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	0.00 (0.00-0.00)	0-0.00	200 (100.0%)	0 (0.0%)
Left-main disease trials	n=2/N=1			n = 650	
Time of primary endpoint assessment in months*	2/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	2/ 1	5.54 (5.52-5.56)	6-5.56	650 (100.0%)	36 (5.5%)
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	2/ 1	2.00 (1.23-2.78)	1-2.78	650 (100.0%)	13 (2.0%)
Target Lesion Revascularisation (% per 100 person years)	2/ 1	10.00 (8.90-11.11)	9-11.11	650 (100.0%)	65 (10.0%)
Definite Stent Thrombosis (% per 100 person years)	2/ 1	0.62 (0.61-0.62)	1-0.62	650 (100.0%)	4 (0.6%)
Saphenuous vein graft lesions trials	n=0/N=0			n = 0	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
In-stent restenose lesions trials	n=1/N=1			n = 66	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Bifurcation lesions trials	n=2/N=2			n = 443	
Time of primary endpoint assessment in months*	1/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	1/ 1	0.68 (0.68-0.68)	1-0.68	293 (66.1%)	1 (0.3%)
Cardiac Death (% per 100 person years)	2/ 2	0.78 (0.68-0.89)	1-0.89	443 (100.0%)	2 (0.5%)
Myocardial Infarction (% per 100 person years)	2/ 2	3.34 (1.35-5.33)	1-5.33	443 (100.0%)	8 (1.8%)
Target Lesion Revascularisation (% per 100 person years)	1/ 1	3.38 (3.38-3.38)	3-3.38	293 (66.1%)	5 (1.7%)
Definite Stent Thrombosis (% per 100 person years)	2/ 2	0.00 (0.00-0.00)	0-0.00	443 (100.0%)	0 (0.0%)
Chronic total occlusion lesions trials	n=3/N=3			n = 464	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	2/ 2	0.96 (0.00-1.92)	0-1.92	304 (65.5%)	2 (0.7%)
Cardiac Death (% per 100 person years)	2/ 2	0.00 (0.00-0.00)	0-0.00	304 (65.5%)	0 (0.0%)
Myocardial Infarction (% per 100 person years)	2/ 2	3.14 (1.92-4.35)	2-4.35	304 (65.5%)	4 (1.3%)
Target Lesion Revascularisation (% per 100 person years)	2/ 2	9.53 (3.85-15.22)	4-15.22	304 (65.5%)	11 (3.6%)
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

*months

TABLE S16. NEW DES ANGIOGRAPHIC OUTCOMES BY PATIENT AND LESION SUBGROUP

	Nr of contributing Arms/Trials	Median (IQR)	Range	Nr of contributing patients (% of subgroup)
All comers trials	n=22/N=16			n = 38038
N of arms/trials reporting any angiographic endpoint	9/ 6			
Time of angiographic endpoint assessment (months)	9/ 6	8 (8-9)	6-13	3304 (8.7%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	9/ 6	2.30 (2.20-2.34)	2.04 to 2.44	3304 (8.7%)
In-stent Late Lumen Loss (mean mm)	9/ 6	0.17 (0.16-0.23)	0.13 to 0.27	3304 (8.7%)
In-segment Binary Restenosis (%)	9/ 6	6.70 (5.20-7.50)	3.90 to 11.60	3304 (8.7%)
In-segment Percentual Diameter Stenosis (mean %)	9/ 6	24.10 (23.30-27.10)	21.99 to 30.90	3304 (8.7%)
STEMI trials	n=7/N=7			n = 4645
N of arms/trials reporting any angiographic endpoint	4/ 4			
Time of angiographic endpoint assessment (months)	4/ 4	9 (7-9)	6-9	261 (5.6%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	3/ 3	1.88 (1.84-2.18)	1.84 to 2.18	147 (3.2%)
In-stent Late Lumen Loss (mean mm)	4/ 4	0.64 (0.54-0.71)	0.49 to 0.73	261 (5.6%)
In-segment Binary Restenosis (%)	4/ 4	13.50 (12.75-14.95)	12.50 to 15.90	261 (5.6%)
In-segment Percentual Diameter Stenosis (mean %)	4/ 4	31.00 (28.75-34.80)	27.50 to 37.60	261 (5.6%)
Diabetes trials	n=7/N=7			n = 1646
N of arms/trials reporting any angiographic endpoint	6/ 6			
Time of angiographic endpoint assessment (months)	6/ 6	9 (9-9)	8-10	643 (39.1%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	4/ 4	2.25 (1.88-2.56)	1.80 to 2.57	386 (23.5%)
In-stent Late Lumen Loss (mean mm)	6/ 6	0.20 (0.13-0.63)	0.11 to 0.74	643 (39.1%)
In-segment Binary Restenosis (%)	5/ 5	2.20 (1.20-17.90)	0.90 to 18.00	425 (25.8%)
In-segment Percentual Diameter Stenosis (mean %)	5/ 5	22.42 (21.90-32.90)	17.20 to 42.00	604 (36.7%)
Elderlies trials (mean age≥75 years)	n=1/N=1			n = 800
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (0.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Multivessel disease trials	n=1/N=1			n = 200
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	90 (45.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.29 (2.29-2.29)	2.29 to 2.29	90 (45.0%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.05 (0.05-0.05)	0.05 to 0.05	90 (45.0%)

In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	26.87 (26.87-26.87)	26.87 to 26.87	90 (45.0%)
Left-main disease trials	n=2/N=1			n = 650
N of arms/trials reporting any angiographic endpoint	2/ 1			
Time of angiographic endpoint assessment (months)	2/ 1	7 (7-7)	7-7	463 (71.2%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	2/ 1	19.15 (16.80-21.50)	16.80 to 21.50	463 (71.2%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Saphenuous vein graft lesions trials	n=0/N=0			n = 0
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (.%)
Angio endpoints				
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (.%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (.%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (.%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (.%)
In-stent restenose lesions trials	n=1/N=1			n = 66
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	21 (31.8%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	1/ 1	14.30 (14.30-14.30)	14.30 to 14.30	21 (31.8%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Bifurcation lesions trials	n=2/N=2			n = 443
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	1/ 1	18 (18-18)	18-18	75 (16.9%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Chronic total occlusion lesions trials	n=3/N=3			n = 464
N of arms/trials reporting any angiographic endpoint	3/ 3			
Time of angiographic endpoint assessment (months)	3/ 3	8 (8-9)	8-9	192 (41.4%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 2	2.14 (1.89-2.39)	1.89 to 2.39	121 (26.1%)
In-stent Late Lumen Loss (mean mm)	2/ 2	0.29 (0.05-0.54)	0.05 to 0.54	121 (26.1%)
In-segment Binary Restenosis (%)	3/ 3	11.10 (7.10-14.10)	7.10 to 14.10	192 (41.4%)
In-segment Percentual Diameter Stenosis (mean %)	3/ 3	30.60 (30.40-33.37)	30.40 to 33.37	192 (41.4%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

TABLE S17. FDA APPROVED NEW DES CLINICAL OUTCOMES BY PATIENT AND LESION SUBGROUP

	Nr of contributing Arms/Trials	Rate per 100 person years	Range	Nr of contributing patients (% of subgroup)	Nr of events (%)
All comers trials	n=14/N=12			n = 22822	
Time of primary endpoint assessment in months*	9/ 8	12 (12-12)	9-24		
All-cause Death (% per 100 person years)	12/ 10	2.24 (1.61-2.78)	1-3.45	19505 (85.5%)	253 (1.3%)
Cardiac Death (% per 100 person years)	12/ 10	1.15 (0.92-1.51)	1-2.59	19505 (85.5%)	152 (0.8%)
Myocardial Infarction (% per 100 person years)	12/ 10	2.87 (1.66-3.47)	0-13.59	19505 (85.5%)	502 (2.6%)
Target Lesion Revascularisation (% per 100 person years)	11/ 9	1.92 (1.52-3.37)	1-4.07	17191 (75.3%)	275 (1.6%)
Definite Stent Thrombosis (% per 100 person years)	11/ 9	0.27 (0.13-0.44)	0-1.16	19105 (83.7%)	37 (0.2%)
STEMI trials	n=1/N=1			n = 1504	
Time of primary endpoint assessment in months*	1/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	1/ 1	3.46 (3.46-3.46)	3-3.46	1504 (100.0%)	26 (1.7%)
Cardiac Death (% per 100 person years)	1/ 1	3.20 (3.20-3.20)	3-3.20	1504 (100.0%)	24 (1.6%)
Myocardial Infarction (% per 100 person years)	1/ 1	1.33 (1.33-1.33)	1-1.33	1504 (100.0%)	10 (0.7%)
Target Lesion Revascularisation (% per 100 person years)	1/ 1	2.13 (2.13-2.13)	2-2.13	1504 (100.0%)	16 (1.1%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	0.53 (0.53-0.53)	1-0.53	1504 (100.0%)	4 (0.3%)
Diabetes trials	n=4/N=4			n = 1053	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	2/ 2	0.70 (0.00-1.40)	0-1.40	580 (55.1%)	3 (0.5%)
Cardiac Death (% per 100 person years)	2/ 2	0.23 (0.00-0.47)	0-0.47	580 (55.1%)	1 (0.2%)
Myocardial Infarction (% per 100 person years)	2/ 2	2.02 (0.79-3.26)	1-3.26	580 (55.1%)	8 (1.4%)
Target Lesion Revascularisation (% per 100 person years)	2/ 2	5.67 (1.57-9.77)	2-9.77	580 (55.1%)	23 (4.0%)
Definite Stent Thrombosis (% per 100 person years)	2/ 2	0.00 (0.00-0.00)	0-0.00	580 (55.1%)	0 (0.0%)
Elderlies trials (mean age≥75 years)	n=1/N=1			n = 800	
Time of primary endpoint assessment in months*	1/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	1/ 1	8.52 (8.52-8.52)	9-8.52	800 (100.0%)	34 (4.3%)
Cardiac Death (% per 100 person years)	1/ 1	3.26 (3.26-3.26)	3-3.26	800 (100.0%)	13 (1.6%)
Myocardial Infarction (% per 100 person years)	1/ 1	4.26 (4.26-4.26)	4-4.26	800 (100.0%)	17 (2.1%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	0.50 (0.50-0.50)	1-0.50	800 (100.0%)	2 (0.3%)
Multivessel disease trials	n=1/N=1			n = 200	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	1/ 1	1.01 (1.01-1.01)	1-1.01	200 (100.0%)	1 (0.5%)
Cardiac Death (% per 100 person years)	1/ 1	1.01 (1.01-1.01)	1-1.01	200 (100.0%)	1 (0.5%)

Myocardial Infarction (% per 100 person years)	1/ 1	1.01 (1.01-1.01)	1-1.01	200 (100.0%)	1 (0.5%)
Target Lesion Revascularisation (% per 100 person years)	1/ 1	6.06 (6.06-6.06)	6-6.06	200 (100.0%)	6 (3.0%)
Definite Stent Thrombosis (% per 100 person years)	1/ 1	0.00 (0.00-0.00)	0-0.00	200 (100.0%)	0 (0.0%)
Left-main disease trials	n=2/N=1			n = 650	
Time of primary endpoint assessment in months*	2/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	2/ 1	5.54 (5.52-5.56)	6-5.56	650 (100.0%)	36 (5.5%)
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	2/ 1	2.00 (1.23-2.78)	1-2.78	650 (100.0%)	13 (2.0%)
Target Lesion Revascularisation (% per 100 person years)	2/ 1	10.00 (8.90-11.11)	9-11.11	650 (100.0%)	65 (10.0%)
Definite Stent Thrombosis (% per 100 person years)	2/ 1	0.62 (0.61-0.62)	1-0.62	650 (100.0%)	4 (0.6%)
Saphenuous vein graft lesions trials	n=0/N=0			n = 0	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (.%)	0 (.%)
In-stent restenose lesions trials	n=1/N=1			n = 66	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)
Bifurcation lesions trials	n=2/N=2			n = 443	
Time of primary endpoint assessment in months*	1/ 1	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	1/ 1	0.68 (0.68-0.68)	1-0.68	293 (66.1%)	1 (0.3%)
Cardiac Death (% per 100 person years)	2/ 2	0.78 (0.68-0.89)	1-0.89	443 (100.0%)	2 (0.5%)
Myocardial Infarction (% per 100 person years)	2/ 2	3.34 (1.35-5.33)	1-5.33	443 (100.0%)	8 (1.8%)
Target Lesion Revascularisation (% per 100 person years)	1/ 1	3.38 (3.38-3.38)	3-3.38	293 (66.1%)	5 (1.7%)
Definite Stent Thrombosis (% per 100 person years)	2/ 2	0.00 (0.00-0.00)	0-0.00	443 (100.0%)	0 (0.0%)
Chronic total occlusion lesions trials	n=1/N=1			n = 207	
Time of primary endpoint assessment in months*	0/ 0	(-)	-		
All-cause Death (% per 100 person years)	1/ 1	1.92 (1.92-1.92)	2-1.92	207 (100.0%)	2 (1.0%)
Cardiac Death (% per 100 person years)	1/ 1	0.00 (0.00-0.00)	0-0.00	207 (100.0%)	0 (0.0%)
Myocardial Infarction (% per 100 person years)	1/ 1	1.92 (1.92-1.92)	2-1.92	207 (100.0%)	2 (1.0%)
Target Lesion Revascularisation (% per 100 person years)	1/ 1	3.85 (3.85-3.85)	4-3.85	207 (100.0%)	4 (1.9%)
Definite Stent Thrombosis (% per 100 person years)	0/ 0	(-)	-	0 (0.0%)	0 (.%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

*months

TABLE S18. FDA APPROVED NEW DES ANGIOGRAPHIC OUTCOMES BY PATIENT AND LESION SUBGROUP

	Nr of contributing Arms/Trials	Median (IQR)	Range	Nr of contributing patients (% of subgroup)
All comers trials	n=14/N=12			n = 22822
N of arms/trials reporting any angiographic endpoint	6/ 5			
Time of angiographic endpoint assessment (months)	6/ 5	9 (8-13)	6-13	1586 (6.9%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	6/ 5	2.31 (2.20-2.42)	2.07 to 2.44	1586 (6.9%)
In-stent Late Lumen Loss (mean mm)	6/ 5	0.17 (0.16-0.23)	0.14 to 0.27	1586 (6.9%)
In-segment Binary Restenosis (%)	6/ 5	5.85 (5.10-7.50)	3.90 to 10.10	1586 (6.9%)
In-segment Percentual Diameter Stenosis (mean %)	6/ 5	23.70 (22.99-24.30)	21.99 to 29.20	1586 (6.9%)
STEMI trials	n=1/N=1			n = 1504
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (0.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Diabetes trials	n=4/N=4			n = 1053
N of arms/trials reporting any angiographic endpoint	4/ 4			
Time of angiographic endpoint assessment (months)	4/ 4	9 (9-9)	8-9	491 (46.6%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 2	2.56 (2.54-2.57)	2.54 to 2.57	234 (22.2%)
In-stent Late Lumen Loss (mean mm)	4/ 4	0.16 (0.12-0.20)	0.11 to 0.22	491 (46.6%)
In-segment Binary Restenosis (%)	3/ 3	1.20 (0.90-2.20)	0.90 to 2.20	273 (25.9%)
In-segment Percentual Diameter Stenosis (mean %)	3/ 3	21.90 (17.20-22.42)	17.20 to 22.42	452 (42.9%)
Elderlies trials (mean age≥75 years)	n=1/N=1			n = 800
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (0.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Multivessel disease trials	n=1/N=1			n = 200
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	90 (45.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.29 (2.29-2.29)	2.29 to 2.29	90 (45.0%)

In-stent Late Lumen Loss (mean mm)	1/ 1	0.05 (0.05-0.05)	0.05 to 0.05	90 (45.0%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	26.87 (26.87-26.87)	26.87 to 26.87	90 (45.0%)
Left-main disease trials	n=2/N=1			n = 650
N of arms/trials reporting any angiographic endpoint	2/ 1			
Time of angiographic endpoint assessment (months)	2/ 1	7 (7-7)	7-7	463 (71.2%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	2/ 1	19.15 (16.80-21.50)	16.80 to 21.50	463 (71.2%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Saphenuous vein graft lesions trials	n=0/N=0			n = 0
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (.%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (.%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (.%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (.%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (.%)
In-stent restenose lesions trials	n=1/N=1			n = 66
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	21 (31.8%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	1/ 1	14.30 (14.30-14.30)	14.30 to 14.30	21 (31.8%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Bifurcation lesions trials	n=2/N=2			n = 443
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	1/ 1	18 (18-18)	18-18	75 (16.9%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-stent Late Lumen Loss (mean mm)	0/ 0	(-)	to	0 (0.0%)
In-segment Binary Restenosis (%)	0/ 0	(-)	to	0 (0.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0	(-)	to	0 (0.0%)
Chronic total occlusion lesions trials	n=1/N=1			n = 207
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	8 (8-8)	8-8	85 (41.1%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.39 (2.39-2.39)	2.39 to 2.39	85 (41.1%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.05 (0.05-0.05)	0.05 to 0.05	85 (41.1%)
In-segment Binary Restenosis (%)	1/ 1	7.10 (7.10-7.10)	7.10 to 7.10	85 (41.1%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	30.40 (30.40-30.40)	30.40 to 30.40	85 (41.1%)

Data reported as number of trials (% total nr of trials of the subgroup), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients of the subgroup).

TABLE S19. CLINICAL OUTCOMES OF SPECIFIC DES TYPES

	Nr of contributing arms (% of brand arms)	Rate per 100 person years	Range	Nr of contributing patients (% of brand)	Nr of events (%)
Amazonia PAX n = 1 arms / N = 1 trials				n = 15	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
BioFreedom n = 2 arms* / N = 1 trials				n = 122	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	2 (100.00)	0.00	0-0.00	122 (100.0%)	0 (0.0%)
Cardiac Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
BioMatrix n = 4 arms / N = 4 trials				n = 1615	
Time of primary endpoint assessment in months	2 (50.00)	11 (9-12)	9-12		
All-cause Death (% per 100 person years)	3 (75.00)	3.13 (0.00-3.42)	0-3.42	1515 (93.8%)	40 (2.6%)
Cardiac Death (% per 100 person years)	3 (75.00)	2.18 (0.00-2.78)	0-2.78	1535 (95.0%)	30 (2.0%)
Myocardial Infarction (% per 100 person years)	4 (100.00)	3.50 (1.96-6.31)	2-7.62	1615 (100.0%)	64 (4.0%)
Target Lesion Revascularisation (% per 100 person years)	4 (100.00)	2.03 (0.78-4.13)	0-5.76	1615 (100.0%)	47 (2.9%)
Definite Stent Thrombosis (% per 100 person years)	4 (100.00)	1.68 (0.43-2.49)	0-2.50	1615 (100.0%)	22 (1.4%)
Combo n = 1 arms / N = 1 trials				n = 124	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Coracto SES n = 1 arms / N = 1 trials				n = 48	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	48 (100.0%)	0 (0.0%)
Cardiac Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)

Myocardial Infarction (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	48 (100.0%)	0 (0.0%)
Target Lesion Revascularisation (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Coroflex Please PES n = 2 arms / N = 2 trials				n = 790	
Time of primary endpoint assessment in months	1 (50.00)	9 (9-9)	9-9		
All-cause Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	1 (50.00)	2.32 (2.32-2.32)	2-2.32	631 (79.9%)	11 (1.7%)
Myocardial Infarction (% per 100 person years)	1 (50.00)	6.55 (6.55-6.55)	7-6.55	631 (79.9%)	31 (4.9%)
Target Lesion Revascularisation (% per 100 person years)	1 (50.00)	18.81 (18.81-18.81)	19-18.81	631 (79.9%)	89 (14.1%)
Definite Stent Thrombosis (% per 100 person years)	1 (50.00)	2.22 (2.22-2.22)	2-2.22	631 (79.9%)	14 (2.2%)
Cre8 n = 1 arms / N = 1 trials				n = 162	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	1 (100.00)	1.35 (1.35-1.35)	1-1.35	162 (100.0%)	2 (1.2%)
Cardiac Death (% per 100 person years)	1 (100.00)	1.35 (1.35-1.35)	1-1.35	162 (100.0%)	2 (1.2%)
Myocardial Infarction (% per 100 person years)	1 (100.00)	0.68 (0.68-0.68)	1-0.68	162 (100.0%)	1 (0.6%)
Target Lesion Revascularisation (% per 100 person years)	1 (100.00)	2.70 (2.70-2.70)	3-2.70	162 (100.0%)	4 (2.5%)
Definite Stent Thrombosis (% per 100 person years)	1 (100.00)	0.63 (0.63-0.63)	1-0.63	162 (100.0%)	1 (0.6%)
Cypher n = 87 arms / N = 87 trials				n = 27254	
Time of primary endpoint assessment in months	32 (36.78)	12 (9-12)	6-36		
All-cause Death (% per 100 person years)	57 (65.52)	1.97 (0.97-2.59)	0-12.07	22881 (84.0%)	584 (2.6%)
Cardiac Death (% per 100 person years)	50 (57.47)	0.89 (0.34-1.97)	0-5.00	21854 (80.2%)	318 (1.5%)
Myocardial Infarction (% per 100 person years)	65 (74.71)	2.25 (0.93-4.26)	0-15.79	23646 (86.8%)	1153 (4.9%)
Target Lesion Revascularisation (% per 100 person years)	55 (63.22)	3.20 (1.72-7.13)	0-18.00	20490 (75.2%)	711 (3.5%)
Definite Stent Thrombosis (% per 100 person years)	46 (52.87)	0.65 (0.00-1.13)	0-4.80	19959 (73.2%)	170 (0.9%)
DESyne BD n = 1 arms / N = 1 trials				n = 111	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
DESyne Nx n = 1 arms / N = 1 trials				n = 139	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	139 (100.0%)	0 (0.0%)
Cardiac Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	1 (100.00)	2.88 (2.88-2.88)	3-2.88	139 (100.0%)	3 (2.2%)
Target Lesion Revascularisation (% per 100 person years)	1 (100.00)	2.88 (2.88-2.88)	3-2.88	139 (100.0%)	3 (2.2%)
Definite Stent Thrombosis (% per 100 person years)	1 (100.00)	0.96 (0.96-0.96)	1-0.96	139 (100.0%)	1 (0.7%)

Endeavor n = 21 arms / N = 21 trials				n = 10398	
Time of primary endpoint assessment in months	10 (47.62)	12 (9-36)	6-36		
All-cause Death (% per 100 person years)	12 (57.14)	1.48 (0.78-3.16)	0-3.64	8898 (85.6%)	265 (3.0%)
Cardiac Death (% per 100 person years)	12 (57.14)	0.98 (0.55-1.79)	0-5.35	9281 (89.3%)	161 (1.7%)
Myocardial Infarction (% per 100 person years)	14 (66.67)	1.90 (1.25-3.60)	0-5.32	9427 (90.7%)	746 (7.9%)
Target Lesion Revascularisation (% per 100 person years)	11 (52.38)	5.44 (1.90-6.08)	2-15.22	8125 (78.1%)	418 (5.1%)
Definite Stent Thrombosis (% per 100 person years)	10 (47.62)	0.63 (0.42-0.89)	0-1.82	8778 (84.4%)	62 (0.7%)
Eucatax PES n = 1 arms / N = 1 trials				n = 211	
Time of primary endpoint assessment in months	1 (100.00)	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	1 (100.00)	2.37 (2.37-2.37)	2-2.37	211 (100.0%)	5 (2.4%)
Cardiac Death (% per 100 person years)	1 (100.00)	1.90 (1.90-1.90)	2-1.90	211 (100.0%)	4 (1.9%)
Myocardial Infarction (% per 100 person years)	1 (100.00)	2.84 (2.84-2.84)	3-2.84	211 (100.0%)	6 (2.8%)
Target Lesion Revascularisation (% per 100 person years)	1 (100.00)	6.16 (6.16-6.16)	6-6.16	211 (100.0%)	13 (6.2%)
Definite Stent Thrombosis (% per 100 person years)	1 (100.00)	1.42 (1.42-1.42)	1-1.42	211 (100.0%)	3 (1.4%)
Firebird n = 1 arms / N = 1 trials				n = 224	
Time of primary endpoint assessment in months	1 (100.00)	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	1 (100.00)	1.89 (1.89-1.89)	2-1.89	224 (100.0%)	4 (1.8%)
Myocardial Infarction (% per 100 person years)	1 (100.00)	3.30 (3.30-3.30)	3-3.30	224 (100.0%)	7 (3.1%)
Target Lesion Revascularisation (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	1 (100.00)	0.94 (0.94-0.94)	1-0.94	224 (100.0%)	2 (0.9%)
Infinnium n = 1 arms / N = 1 trials				n = 111	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Janus n = 2 arms / N = 2 trials				n = 266	
Time of primary endpoint assessment in months	1 (50.00)	8 (8-8)	8-8		
All-cause Death (% per 100 person years)	1 (50.00)	1.24 (1.24-1.24)	1-1.24	166 (62.4%)	1 (0.6%)
Cardiac Death (% per 100 person years)	1 (50.00)	1.24 (1.24-1.24)	1-1.24	166 (62.4%)	1 (0.6%)
Myocardial Infarction (% per 100 person years)	1 (50.00)	2.48 (2.48-2.48)	2-2.48	166 (62.4%)	2 (1.2%)
Target Lesion Revascularisation (% per 100 person years)	2 (100.00)	8.12 (7.45-8.78)	7-8.78	266 (100.0%)	12 (4.5%)
Definite Stent Thrombosis (% per 100 person years)	1 (50.00)	0.00 (0.00-0.00)	0-0.00	166 (62.4%)	0 (0.0%)
Luc Chopin 2 n = 1 arms / N = 1 trials				n = 25	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	25 (100.0%)	0 (0.0%)

Cardiac Death (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	25 (100.0%)	0 (0.0%)
Myocardial Infarction (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	25 (100.0%)	0 (0.0%)
Target Lesion Revascularisation (% per 100 person years)	1 (100.00)	26.67 (26.67-26.67)	27-26.67	25 (100.0%)	5 (20.0%)
Definite Stent Thrombosis (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	25 (100.0%)	0 (0.0%)
Nevo n = 1 arms / N = 1 trials				n = 202	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	1 (100.00)	1.01 (1.01-1.01)	1-1.01	202 (100.0%)	1 (0.5%)
Cardiac Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	1 (100.00)	4.04 (4.04-4.04)	4-4.04	202 (100.0%)	4 (2.0%)
Target Lesion Revascularisation (% per 100 person years)	1 (100.00)	3.03 (3.03-3.03)	3-3.03	202 (100.0%)	3 (1.5%)
Definite Stent Thrombosis (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	202 (100.0%)	0 (0.0%)
Nobori n = 7 arms / N = 7 trials				n = 5092	
Time of primary endpoint assessment in months	4 (57.14)	11 (9-12)	9-12		
All-cause Death (% per 100 person years)	6 (85.71)	1.54 (1.40-2.39)	0-2.54	5077 (99.7%)	94 (1.9%)
Cardiac Death (% per 100 person years)	5 (71.43)	0.78 (0.78-0.87)	1-1.55	4992 (98.0%)	49 (1.0%)
Myocardial Infarction (% per 100 person years)	6 (85.71)	3.99 (2.84-5.61)	2-6.27	5077 (99.7%)	138 (2.7%)
Target Lesion Revascularisation (% per 100 person years)	6 (85.71)	1.38 (0.00-2.91)	0-3.25	5077 (99.7%)	115 (2.3%)
Definite Stent Thrombosis (% per 100 person years)	6 (85.71)	0.12 (0.00-0.72)	0-0.98	5077 (99.7%)	26 (0.5%)
Pico Elite PES n = 1 arms / N = 1 trials				n = 20	
Time of primary endpoint assessment in months	1 (100.00)	1 (1-1)	1-1		
All-cause Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Promus Element n = 3 arms / N = 3 trials				n = 1016	
Time of primary endpoint assessment in months	2 (66.67)	7 (1-12)	1-12		
All-cause Death (% per 100 person years)	3 (100.00)	1.34 (0.00-2.64)	0-2.64	1016 (100.0%)	17 (1.7%)
Cardiac Death (% per 100 person years)	3 (100.00)	0.75 (0.00-0.94)	0-0.94	1016 (100.0%)	9 (0.9%)
Myocardial Infarction (% per 100 person years)	3 (100.00)	1.07 (0.00-3.40)	0-3.40	1016 (100.0%)	17 (1.7%)
Target Lesion Revascularisation (% per 100 person years)	3 (100.00)	1.51 (0.00-1.88)	0-1.88	1016 (100.0%)	18 (1.8%)
Definite Stent Thrombosis (% per 100 person years)	2 (66.67)	0.20 (0.00-0.41)	0-0.41	918 (90.4%)	3 (0.3%)
Resolute n = 8 arms / N = 8 trials				n = 3840	
Time of primary endpoint assessment in months	4 (50.00)	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	8 (100.00)	1.77 (0.91-3.43)	0-5.56	3840 (100.0%)	104 (2.7%)
Cardiac Death (% per 100 person years)	7 (87.50)	1.01 (0.00-1.34)	0-1.80	3516 (91.6%)	43 (1.2%)
Myocardial Infarction (% per 100 person years)	8 (100.00)	3.68 (2.35-8.10)	1-13.49	3840 (100.0%)	269 (7.0%)
Target Lesion Revascularisation (% per 100 person years)	8 (100.00)	3.29 (1.59-6.97)	2-11.11	3840 (100.0%)	212 (5.5%)

Definite Stent Thrombosis (% per 100 person years)	5 (62.50)	0.58 (0.40-0.62)	0-1.16	3288 (85.6%)	23 (0.7%)
SimvES n = 1 arms / N = 1 trials				n = 14	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	14 (100.0%)	0 (0.0%)
Cardiac Death (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	14 (100.0%)	0 (0.0%)
Myocardial Infarction (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	14 (100.0%)	0 (0.0%)
Target Lesion Revascularisation (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	1 (100.00)	0.00 (0.00-0.00)	0-0.00	14 (100.0%)	0 (0.0%)
Supralimus n = 1 arms / N = 1 trials				n = 106	
Time of primary endpoint assessment in months	0 (0.00)	(-)	-		
All-cause Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Cardiac Death (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Myocardial Infarction (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Target Lesion Revascularisation (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Definite Stent Thrombosis (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Synergy n = 2 arms / N = 1 trials				n = 193	
Time of primary endpoint assessment in months	2 (100.00)	1 (1-1)	1-1		
All-cause Death (% per 100 person years)	2 (100.00)	0.00 (0.00-0.00)	0-0.00	193 (100.0%)	0 (0.0%)
Cardiac Death (% per 100 person years)	2 (100.00)	0.00 (0.00-0.00)	0-0.00	193 (100.0%)	0 (0.0%)
Myocardial Infarction (% per 100 person years)	2 (100.00)	24.56 (12.77-36.36)	13-36.36	193 (100.0%)	4 (2.1%)
Target Lesion Revascularisation (% per 100 person years)	2 (100.00)	0.00 (0.00-0.00)	0-0.00	193 (100.0%)	0 (0.0%)
Definite Stent Thrombosis (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Taxus n = 68 arms / N = 68 trials				n = 19143	
Time of primary endpoint assessment in months	27 (39.71)	12 (9-12)	1-36		
All-cause Death (% per 100 person years)	46 (67.65)	1.60 (1.00-3.46)	0-10.26	14997 (78.3%)	306 (2.0%)
Cardiac Death (% per 100 person years)	46 (67.65)	1.07 (0.50-2.67)	0-10.26	16030 (83.7%)	219 (1.4%)
Myocardial Infarction (% per 100 person years)	53 (77.94)	3.42 (1.95-5.32)	0-18.87	16642 (86.9%)	649 (3.9%)
Target Lesion Revascularisation (% per 100 person years)	50 (73.53)	5.51 (3.53-9.23)	0-17.53	14995 (78.3%)	762 (5.1%)
Definite Stent Thrombosis (% per 100 person years)	41 (60.29)	0.68 (0.00-1.19)	0-4.29	13799 (72.1%)	157 (1.1%)
Taxus Element n = 1 arms / N = 1 trials				n = 942	
Time of primary endpoint assessment in months	1 (100.00)	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	1 (100.00)	0.65 (0.65-0.65)	1-0.65	942 (100.0%)	6 (0.6%)
Cardiac Death (% per 100 person years)	1 (100.00)	0.54 (0.54-0.54)	1-0.54	942 (100.0%)	5 (0.5%)
Myocardial Infarction (% per 100 person years)	1 (100.00)	2.17 (2.17-2.17)	2-2.17	942 (100.0%)	20 (2.1%)
Target Lesion Revascularisation (% per 100 person years)	1 (100.00)	3.80 (3.80-3.80)	4-3.80	942 (100.0%)	35 (3.7%)
Definite Stent Thrombosis (% per 100 person years)	0 (0.00)	(-)	-	0 (0.0%)	0 (.%)
Xience n = 20 arms / N = 20 trials				n = 5425	
Time of primary endpoint assessment in months	7 (35.00)	12 (12-12)	12-24		

All-cause Death (% per 100 person years)	13 (65.00)	2.44 (1.22-3.02)	0-8.52	5032 (92.8%)	174 (3.5%)
Cardiac Death (% per 100 person years)	14 (70.00)	0.99 (0.76-1.69)	0-3.26	4859 (89.6%)	95 (2.0%)
Myocardial Infarction (% per 100 person years)	16 (80.00)	1.61 (0.45-4.80)	0-13.59	5235 (96.5%)	247 (4.7%)
Target Lesion Revascularisation (% per 100 person years)	13 (65.00)	3.37 (2.01-6.00)	0-8.90	4747 (87.5%)	168 (3.5%)
Definite Stent Thrombosis (% per 100 person years)	15 (75.00)	0.20 (0.00-0.53)	0-2.20	4831 (89.1%)	28 (0.6%)
Xience/Promus n = 17 arms / N = 17 trials				n = 14296	
Time of primary endpoint assessment in months	10 (58.82)	12 (12-12)	9-24		
All-cause Death (% per 100 person years)	13 (76.47)	1.40 (0.98-2.01)	0-3.45	12771 (89.3%)	218 (1.7%)
Cardiac Death (% per 100 person years)	13 (76.47)	0.77 (0.47-1.17)	0-2.59	12771 (89.3%)	123 (1.0%)
Myocardial Infarction (% per 100 person years)	13 (76.47)	2.52 (1.44-3.09)	1-9.82	12771 (89.3%)	310 (2.4%)
Target Lesion Revascularisation (% per 100 person years)	12 (70.59)	2.38 (1.83-3.25)	1-9.77	11997 (83.9%)	303 (2.5%)
Definite Stent Thrombosis (% per 100 person years)	12 (70.59)	0.22 (0.03-0.36)	0-0.45	12547 (87.8%)	30 (0.2%)
Yukon Choice PC n = 2 arms / N = 2 trials				n = 1501	
Time of primary endpoint assessment in months	1 (50.00)	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	2 (100.00)	3.30 (1.98-4.62)	2-4.62	1501 (100.0%)	64 (4.3%)
Cardiac Death (% per 100 person years)	1 (50.00)	2.69 (2.69-2.69)	3-2.69	1299 (86.5%)	35 (2.7%)
Myocardial Infarction (% per 100 person years)	2 (100.00)	2.78 (1.49-4.08)	1-4.08	1501 (100.0%)	56 (3.7%)
Target Lesion Revascularisation (% per 100 person years)	2 (100.00)	7.17 (5.94-8.39)	6-8.39	1501 (100.0%)	121 (8.1%)
Definite Stent Thrombosis (% per 100 person years)	2 (100.00)	0.31 (0.00-0.62)	0-0.62	1501 (100.0%)	8 (0.5%)
Yukon Choice PF n = 6 arms / N = 6 trials				n = 2907	
Time of primary endpoint assessment in months	1 (16.67)	12 (12-12)	12-12		
All-cause Death (% per 100 person years)	5 (83.33)	2.40 (1.99-3.55)	1-6.86	2881 (99.1%)	91 (3.2%)
Cardiac Death (% per 100 person years)	3 (50.00)	2.10 (1.85-4.57)	2-4.57	2455 (84.5%)	48 (2.0%)
Myocardial Infarction (% per 100 person years)	4 (66.67)	4.05 (3.19-4.39)	2-4.57	2656 (91.4%)	101 (3.8%)
Target Lesion Revascularisation (% per 100 person years)	4 (66.67)	12.69 (11.22-13.32)	10-13.71	2548 (87.7%)	259 (10.2%)
Definite Stent Thrombosis (% per 100 person years)	4 (66.67)	0.70 (0.25-0.95)	0-1.00	2656 (91.4%)	15 (0.6%)
ZoMaxx n = 2 arms / N = 2 trials				n = 760	
Time of primary endpoint assessment in months	1 (50.00)	9 (9-9)	9-9		
All-cause Death (% per 100 person years)	2 (100.00)	1.76 (1.51-2.01)	2-2.01	760 (100.0%)	9 (1.2%)
Cardiac Death (% per 100 person years)	2 (100.00)	0.25 (0.00-0.50)	0-0.50	760 (100.0%)	2 (0.3%)
Myocardial Infarction (% per 100 person years)	2 (100.00)	5.07 (2.76-7.37)	3-7.37	760 (100.0%)	22 (2.9%)
Target Lesion Revascularisation (% per 100 person years)	2 (100.00)	8.12 (5.52-10.72)	6-10.72	760 (100.0%)	38 (5.0%)
Definite Stent Thrombosis (% per 100 person years)	2 (100.00)	0.84 (0.67-1.00)	1-1.00	760 (100.0%)	5 (0.7%)

Data reported as number of trials (% total nr of trials using the stent brand), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients in the stent brand).

*Two drug concentration tested

TABLE S20. ANGIOGRAPHIC OUTCOMES OF SPECIFIC DES TYPES

	Nr of contributing Arms/Trials	Median (IQR)	Range	Nr of contributing patients (% of brand)
Amazonia PAX n = 1 arms / N = 1 trials				n = 15
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	4		15 (100.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0			
In-stent Late Lumen Loss (mean mm)	1/ 1			15 (100.0%)
In-segment Binary Restenosis (%)	0/ 0			
In-segment Percentual Diameter Stenosis (mean %)	0/ 0			
BioFreedom n = 2 arms* / N = 1 trials				n = 122
N of arms/trials reporting any angiographic endpoint	2/ 1			
Time of angiographic endpoint assessment (months)	2/ 1	12 (12-12)	12-12	122 (100.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0			
In-stent Late Lumen Loss (mean mm)	2/ 1	0.10 (0.08-0.12)	0.08 to 0.12	122 (100.0%)
In-segment Binary Restenosis (%)	0/ 0			
In-segment Percentual Diameter Stenosis (mean %)	0/ 0			
BioMatrix n = 4 arms / N = 4 trials				n = 1615
N of arms/trials reporting any angiographic endpoint	2/ 2			
Time of angiographic endpoint assessment (months)	2/ 2	8 (6-9)	6-9	245 (15.2%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 2	2.44 (2.23-2.64)	2.23 to 2.64	245 (15.2%)
In-stent Late Lumen Loss (mean mm)	2/ 2	0.20 (0.13-0.26)	0.13 to 0.26	245 (15.2%)
In-segment Binary Restenosis (%)	2/ 2	5.30 (3.90-6.70)	3.90 to 6.70	245 (15.2%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 2	24.57 (22.03-27.10)	22.03 to 27.10	245 (15.2%)
Combo n = 1 arms / N = 1 trials				n = 124
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	109 (87.9%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.31 (2.31-2.31)	2.31 to 2.31	109 (87.9%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.39 (0.39-0.39)	0.39 to 0.39	109 (87.9%)
In-segment Binary Restenosis (%)	1/ 1	8.30 (8.30-8.30)	8.30 to 8.30	109 (87.9%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0			
Coracto SES n = 1 arms / N = 1 trials				n = 48
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	6 (6-6)	6-6	46 (95.8%)

in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0			
In-stent Late Lumen Loss (mean mm)	0/ 0			
In-segment Binary Restenosis (%)	1/ 1	17.40 (17.40-17.40)	17.40 to 17.40	46 (95.8%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	31.10 (31.10-31.10)	31.10 to 31.10	46 (95.8%)
Coroflex Please PES n = 2 arms / N = 2 trials				n = 790
N of arms/trials reporting any angiographic endpoint	2/ 2			
Time of angiographic endpoint assessment (months)	2/ 2	9 (9-9)	9-9	516 (65.3%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 2	1.97 (1.82-2.11)	1.82 to 2.11	516 (65.3%)
In-stent Late Lumen Loss (mean mm)	2/ 2	0.63 (0.55-0.71)	0.55 to 0.71	516 (65.3%)
In-segment Binary Restenosis (%)	2/ 2	19.25 (16.30-22.20)	16.30 to 22.20	516 (65.3%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 2	36.42 (34.10-38.75)	34.10 to 38.75	516 (65.3%)
Cre8 n = 1 arms / N = 1 trials				n = 162
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	6 (6-6)	6-6	141 (87.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.50 (2.50-2.50)	2.50 to 2.50	141 (87.0%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.14 (0.14-0.14)	0.14 to 0.14	141 (87.0%)
In-segment Binary Restenosis (%)	1/ 1	3.20 (3.20-3.20)	3.20 to 3.20	141 (87.0%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	20.53 (20.53-20.53)	20.53 to 20.53	141 (87.0%)
Cypher n = 87 arms / N = 87 trials				n = 27254
N of arms/trials reporting any angiographic endpoint	66/ 66			
Time of angiographic endpoint assessment (months)	65/ 65	8 (7-9)	3-18	9306 (34.1%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	53/ 53	2.41 (2.24-2.47)	1.98 to 2.98	8164 (30.0%)
In-stent Late Lumen Loss (mean mm)	59/ 59	0.17 (0.11-0.23)	-0.22 to 0.53	8581 (31.5%)
In-segment Binary Restenosis (%)	63/ 63	6.60 (3.60-10.80)	0.00 to 21.20	9338 (34.3%)
In-segment Percentual Diameter Stenosis (mean %)	57/ 57	23.90 (20.00-28.40)	2.15 to 34.00	8664 (31.8%)
DESyne BD n = 1 arms / N = 1 trials				n = 111
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	6 (6-6)	6-6	111 (100.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0			
In-stent Late Lumen Loss (mean mm)	1/ 1	0.12 (0.12-0.12)	0.12 to 0.12	111 (100.0%)
In-segment Binary Restenosis (%)	1/ 1	0.00 (0.00-0.00)	0.00 to 0.00	111 (100.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0			
DESyne Nx n = 1 arms / N = 1 trials				n = 139
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	125 (89.9%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.36 (2.36-2.36)	2.36 to 2.36	125 (89.9%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.11 (0.11-0.11)	0.11 to 0.11	125 (89.9%)
In-segment Binary Restenosis (%)	1/ 1	5.80 (5.80-5.80)	5.80 to 5.80	125 (89.9%)

In-segment Percentual Diameter Stenosis (mean %)	1/ 1	24.00 (24.00-24.00)	24.00 to 24.00	125 (89.9%)
Endeavor n = 21 arms / N = 21 trials				n = 10398
N of arms/trials reporting any angiographic endpoint	15/ 15			
Time of angiographic endpoint assessment (months)	15/ 15	8 (7-9)	6-10	2281 (21.9%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	12/ 12	1.96 (1.92-2.10)	1.84 to 2.18	2059 (19.8%)
In-stent Late Lumen Loss (mean mm)	14/ 14	0.60 (0.54-0.67)	0.47 to 0.74	2210 (21.3%)
In-segment Binary Restenosis (%)	15/ 15	13.00 (11.10-15.30)	7.90 to 19.30	2281 (21.9%)
In-segment Percentual Diameter Stenosis (mean %)	14/ 14	31.30 (30.00-32.90)	27.50 to 37.60	2244 (21.6%)
Eucatax PES n = 1 arms / N = 1 trials				n = 211
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	75 (35.5%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0			
In-stent Late Lumen Loss (mean mm)	1/ 1	0.52 (0.52-0.52)	0.52 to 0.52	75 (35.5%)
In-segment Binary Restenosis (%)	1/ 1	13.20 (13.20-13.20)	13.20 to 13.20	75 (35.5%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	27.40 (27.40-27.40)	27.40 to 27.40	75 (35.5%)
Firebird n = 1 arms / N = 1 trials				n = 224
N of arms/trials reporting any angiographic endpoint	0/ 0			
Time of angiographic endpoint assessment (months)	0/ 0	(-)	-	0 (0.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	0/ 0			
In-stent Late Lumen Loss (mean mm)	0/ 0			
In-segment Binary Restenosis (%)	0/ 0			
In-segment Percentual Diameter Stenosis (mean %)	0/ 0			
Infinnium n = 1 arms / N = 1 trials				n = 111
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	108 (97.3%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	1.93 (1.93-1.93)	1.93 to 1.93	108 (97.3%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.54 (0.54-0.54)	0.54 to 0.54	108 (97.3%)
In-segment Binary Restenosis (%)	1/ 1	8.30 (8.30-8.30)	8.30 to 8.30	108 (97.3%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	31.10 (31.10-31.10)	31.10 to 31.10	108 (97.3%)
Janus n = 2 arms / N = 2 trials				n = 266
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	6 (6-6)	6-6	153 (57.5%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	1.84 (1.84-1.84)	1.84 to 1.84	153 (57.5%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.65 (0.65-0.65)	0.65 to 0.65	153 (57.5%)
In-segment Binary Restenosis (%)	1/ 1	12.40 (12.40-12.40)	12.40 to 12.40	153 (57.5%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	34.30 (34.30-34.30)	34.30 to 34.30	153 (57.5%)
Luc Chopin 2 n = 1 arms / N = 1 trials				n = 25
N of arms/trials reporting any angiographic endpoint	1/ 1			

Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	21 (84.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.25 (2.25-2.25)	2.25 to 2.25	21 (84.0%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.59 (0.59-0.59)	0.59 to 0.59	21 (84.0%)
In-segment Binary Restenosis (%)	0/ 0			
In-segment Percentual Diameter Stenosis (mean %)	0/ 0			
Nevo n = 1 arms / N = 1 trials				n = 202
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	6 (6-6)	6-6	186 (92.1%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.40 (2.40-2.40)	2.40 to 2.40	186 (92.1%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.13 (0.13-0.13)	0.13 to 0.13	186 (92.1%)
In-segment Binary Restenosis (%)	1/ 1	3.20 (3.20-3.20)	3.20 to 3.20	186 (92.1%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	22.00 (22.00-22.00)	22.00 to 22.00	186 (92.1%)
Nobori n = 7 arms / N = 7 trials				n = 5092
N of arms/trials reporting any angiographic endpoint	5/ 5			
Time of angiographic endpoint assessment (months)	5/ 5	8 (8-9)	7-9	654 (12.8%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	5/ 5	2.40 (2.35-2.48)	2.34 to 2.53	654 (12.8%)
In-stent Late Lumen Loss (mean mm)	5/ 5	0.15 (0.12-0.17)	0.11 to 0.31	654 (12.8%)
In-segment Binary Restenosis (%)	5/ 5	2.40 (0.70-7.10)	0.00 to 15.80	654 (12.8%)
In-segment Percentual Diameter Stenosis (mean %)	5/ 5	21.23 (15.70-21.50)	15.42 to 23.80	654 (12.8%)
Pico Elite PES n = 1 arms / N = 1 trials				n = 20
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	6 (6-6)	6-6	17 (85.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.26 (2.26-2.26)	2.26 to 2.26	17 (85.0%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.47 (0.47-0.47)	0.47 to 0.47	17 (85.0%)
In-segment Binary Restenosis (%)	1/ 1	10.00 (10.00-10.00)	10.00 to 10.00	17 (85.0%)
In-segment Percentual Diameter Stenosis (mean %)	0/ 0			
Promus Element n = 3 arms / N = 3 trials				n = 1016
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	6 (6-6)	6-6	95 (9.4%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.29 (2.29-2.29)	2.29 to 2.29	95 (9.4%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.15 (0.15-0.15)	0.15 to 0.15	95 (9.4%)
In-segment Binary Restenosis (%)	1/ 1	5.30 (5.30-5.30)	5.30 to 5.30	95 (9.4%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	22.02 (22.02-22.02)	22.02 to 22.02	95 (9.4%)
Resolute n = 8 arms / N = 8 trials				n = 3840
N of arms/trials reporting any angiographic endpoint	7/ 7			
Time of angiographic endpoint assessment (months)	7/ 7	9 (7-9)	7-13	1627 (42.4%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	6/ 6	2.42 (2.28-2.45)	2.20 to 2.54	1390 (36.2%)
In-stent Late Lumen Loss (mean mm)	6/ 6	0.24 (0.16-0.27)	0.05 to 0.30	1390 (36.2%)

In-segment Binary Restenosis (%)	7/ 7	5.20 (3.90-13.40)	1.20 to 21.50	1627 (42.4%)
In-segment Percentual Diameter Stenosis (mean %)	5/ 5	23.30 (21.99-23.40)	21.90 to 30.40	634 (16.5%)
SimvES n = 1 arms / N = 1 trials				n = 14
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	6 (6-6)	6-6	14 (100.0%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.08 (2.08-2.08)	2.08 to 2.08	14 (100.0%)
In-stent Late Lumen Loss (mean mm)	1/ 1	1.05 (1.05-1.05)	1.05 to 1.05	14 (100.0%)
In-segment Binary Restenosis (%)	1/ 1	0.00 (0.00-0.00)	0.00 to 0.00	14 (100.0%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	33.50 (33.50-33.50)	33.50 to 33.50	14 (100.0%)
Supralimus n = 1 arms / N = 1 trials				n = 106
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	101 (95.3%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.16 (2.16-2.16)	2.16 to 2.16	101 (95.3%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.32 (0.32-0.32)	0.32 to 0.32	101 (95.3%)
In-segment Binary Restenosis (%)	1/ 1	4.00 (4.00-4.00)	4.00 to 4.00	101 (95.3%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	25.40 (25.40-25.40)	25.40 to 25.40	101 (95.3%)
Synergy n = 2 arms / N = 1 trials				n = 193
N of arms/trials reporting any angiographic endpoint	2/ 1			
Time of angiographic endpoint assessment (months)	2/ 1	6 (6-6)	6-6	176 (91.2%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 1	2.43 (2.41-2.45)	2.41 to 2.45	176 (91.2%)
In-stent Late Lumen Loss (mean mm)	2/ 1	0.12 (0.10-0.13)	0.10 to 0.13	176 (91.2%)
In-segment Binary Restenosis (%)	2/ 1	1.70 (1.10-2.30)	1.10 to 2.30	176 (91.2%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 1	19.20 (18.08-20.33)	18.08 to 20.33	176 (91.2%)
Taxus n = 68 arms / N = 68 trials				n = 19143
N of arms/trials reporting any angiographic endpoint	55/ 55			
Time of angiographic endpoint assessment (months)	54/ 54	8 (6-9)	4-13	9149 (47.8%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	44/ 44	2.25 (2.12-2.31)	1.71 to 2.92	7642 (39.9%)
In-stent Late Lumen Loss (mean mm)	49/ 49	0.39 (0.32-0.45)	0.10 to 0.57	8420 (44.0%)
In-segment Binary Restenosis (%)	48/ 48	10.40 (6.75-14.70)	0.00 to 21.70	8984 (46.9%)
In-segment Percentual Diameter Stenosis (mean %)	48/ 48	26.25 (20.80-30.68)	2.11 to 37.00	8805 (46.0%)
Taxus Element n = 1 arms / N = 1 trials				n = 942
N of arms/trials reporting any angiographic endpoint	1/ 1			
Time of angiographic endpoint assessment (months)	1/ 1	9 (9-9)	9-9	256 (27.2%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	1/ 1	2.34 (2.34-2.34)	2.34 to 2.34	256 (27.2%)
In-stent Late Lumen Loss (mean mm)	1/ 1	0.34 (0.34-0.34)	0.34 to 0.34	256 (27.2%)
In-segment Binary Restenosis (%)	1/ 1	8.80 (8.80-8.80)	8.80 to 8.80	256 (27.2%)
In-segment Percentual Diameter Stenosis (mean %)	1/ 1	26.10 (26.10-26.10)	26.10 to 26.10	256 (27.2%)
Xience n = 20 arms / N = 20 trials				n = 5425

N of arms/trials reporting any angiographic endpoint	13/ 13			
Time of angiographic endpoint assessment (months)	13/ 13	8 (7-9)	6-18	1266 (23.3%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	9/ 9	2.48 (2.29-2.55)	2.00 to 2.92	905 (16.7%)
In-stent Late Lumen Loss (mean mm)	10/ 10	0.14 (0.11-0.20)	0.05 to 0.26	944 (17.4%)
In-segment Binary Restenosis (%)	11/ 11	6.50 (4.30-9.10)	0.00 to 16.80	1101 (20.3%)
In-segment Percentual Diameter Stenosis (mean %)	9/ 9	18.80 (12.80-22.99)	7.20 to 37.90	905 (16.7%)
Xience/Promus n = 17 arms / N = 17 trials				n = 14296
N of arms/trials reporting any angiographic endpoint	8/ 8			
Time of angiographic endpoint assessment (months)	8/ 8	8 (6-9)	6-9	2622 (18.3%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	7/ 7	2.33 (2.17-2.43)	2.07 to 2.57	2404 (16.8%)
In-stent Late Lumen Loss (mean mm)	8/ 8	0.17 (0.13-0.20)	0.11 to 0.23	2622 (18.3%)
In-segment Binary Restenosis (%)	7/ 7	5.10 (3.40-7.50)	0.90 to 10.10	2404 (16.8%)
In-segment Percentual Diameter Stenosis (mean %)	8/ 8	23.85 (22.59-24.20)	17.20 to 29.20	2622 (18.3%)
Yukon Choice PC n = 2 arms / N = 2 trials				n = 1501
N of arms/trials reporting any angiographic endpoint	2/ 2			
Time of angiographic endpoint assessment (months)	2/ 2	7 (6-7)	6-7	1489 (99.2%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 2	2.19 (2.04-2.34)	2.04 to 2.34	1489 (99.2%)
In-stent Late Lumen Loss (mean mm)	2/ 2	0.20 (0.17-0.24)	0.17 to 0.24	1489 (99.2%)
In-segment Binary Restenosis (%)	2/ 2	10.30 (9.00-11.60)	9.00 to 11.60	1489 (99.2%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 2	30.25 (29.60-30.90)	29.60 to 30.90	1489 (99.2%)
Yukon Choice PF n = 6 arms / N = 6 trials				n = 2907
N of arms/trials reporting any angiographic endpoint	6/ 6			
Time of angiographic endpoint assessment (months)	6/ 6	7 (7-7)	3-9	2259 (77.7%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	5/ 5	2.12 (2.10-2.23)	1.80 to 2.26	2247 (77.3%)
In-stent Late Lumen Loss (mean mm)	6/ 6	0.39 (0.20-0.48)	0.16 to 0.63	2259 (77.7%)
In-segment Binary Restenosis (%)	6/ 6	13.75 (11.00-16.90)	0.00 to 18.00	2259 (77.7%)
In-segment Percentual Diameter Stenosis (mean %)	4/ 4	32.32 (31.07-37.50)	30.50 to 42.00	711 (24.5%)
ZoMaxx n = 2 arms / N = 2 trials				n = 760
N of arms/trials reporting any angiographic endpoint	2/ 2			
Time of angiographic endpoint assessment (months)	2/ 2	9 (9-9)	9-9	490 (64.5%)
in-stent Minimal Lumen Diameter at FUP (mean mm)	2/ 2	2.11 (2.03-2.18)	2.03 to 2.18	490 (64.5%)
In-stent Late Lumen Loss (mean mm)	2/ 2	0.59 (0.52-0.67)	0.52 to 0.67	490 (64.5%)
In-segment Binary Restenosis (%)	2/ 2	11.20 (5.90-16.50)	5.90 to 16.50	490 (64.5%)
In-segment Percentual Diameter Stenosis (mean %)	2/ 2	31.00 (28.00-34.00)	28.00 to 34.00	490 (64.5%)

Data reported as number of trials (% total nr of trials using the stent brand), medians (25%-75% interquartile ranges) and range; number of contributing patients (% total number of patients in the stent brand).

*Two drug concentration tested

APPENDIX A: SEARCH STRATEGY

CENTRAL AND PUBMED

CENTRAL*			PubMed†	
Search line	**Search Terms**	**No. Citations**	**Search Terms**	**No. Citations**
#1	MeSH descriptor: [Coronary Artery Disease] explode all trees	2496	((((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])) AND (coronar*[tiab] OR revasculari*[tiab] OR "Myocardial Infarction"[tiab] OR ("Myocardial"[tiab] AND "Infarction"[tiab]) OR ("coronary"[All Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR "coronary artery disease"[All Fields]) AND ((("metal"[All Fields]) AND ("stents"[All Fields] OR "stent"[All Fields] OR "stenting"[All Fields])) OR (("drug-eluting"[All Fields] AND "stents"[All Fields]) OR "drug-eluting stents"[All Fields] OR ("drug"[All Fields] AND "eluting"[All Fields] AND "stent"[All Fields]) OR "drug eluting stent"[All Fields]) OR (("coronary"[All Fields]) AND ("stents"[All Fields] OR "stent"[All Fields] OR "stenting")))) AND publisher[sb]	
#2	MeSH descriptor: [Myocardial Infarction] explode all trees	8187		
#3	coronar*:ti (Word variations have been searched)	13048		
#4	coronar*:ab (Word variations have been searched)	18605		
#5	revasculari*:ti (Word variations have been searched)	999		
#6	revasculari*:ab (Word variations have been searched)	3329		
#7	MeSH descriptor: [Stents] explode all trees	3111		
#8	MeSH descriptor: [Drug-Eluting Stents] explode all trees	603		
#9	stent:ti (Word variations have been searched)	1536		
#10	stent:ab (Word variations have been searched)	2178		
#11	#1 or #2 or #3 or #4 or #5 or #6 in Trials	25670		
#12	#7 or #8 or #9 or #10	3993		
#13	#11 and #12 from 2002 to 2013, in Trials	**1576**		**88**

* Search performed in CENTRAL at 14 October 2013; † Top-up search performed in PubMed at 14 October 2013, using the following limit: publication date from 1 January 2011 to 14 October 2013. The Top-up aimed to retrieve citations with publication dates from 1 January 2011 to current, the time window that is incompletely covered by CENTRAL.

MEDLINE AND EMBASE

MEDLINE*†			EMBASE*‡		
Search line	**Search Terms**	**No. Citations**	**Search line**	**Search Terms**	**No. Citations**
1	*stents/ or *drug-eluting stents/	36289	**1**	stent$.ti,ab.	91073
2	stent$.ti,ab.	62843	**2**	*coronary stent/ or *metal stent/ or *stent thrombosis/ or *drug eluting stent/ or *cardiovascular stent/ or *bare metal stent/ or *arterial stent/ or *vascular stent/ or *stent/ or *carotid artery stent/	40427
3	or/1-2	66077	**3**	or/1-2	93372
4	coronar$.ti,ab.	302175	**4**	coronar$.ti,ab.	391478
5	revasculari$.ti,ab.	41242	**5**	revasculari$.ti,ab.	55931
6	*Coronary Artery Disease/	30077	**6**	stent thrombosis/co	2632
7	*Myocardial Infarction/su	2771	**7**	coronary artery disease.sh.	149753
8	or/4-7	326355	**8**	or/4-7	465308
9	randomized controlled trial.pt.	388449	**9**	random$.tw.	862717
10	controlled clinical trial.pt.	89795	**10**	factorial$.tw.	22405
11	randomized.ab.	303425	**11**	(crossover$ or cross-over$).tw.	70534
12	placebo.ab.	163099	**12**	placebo$.tw.	201491
13	drug therapy.fs.	1761402	**13**	(doubl$ adj blind$).tw.	147455
14	randomly.ab.	214741	**14**	(singl$ adj blind$).tw.	14247
15	trial.ab.	319445	**15**	assign$.tw.	236885
16	groups.ab.	1365442	**16**	allocat$.tw.	81550
17	or/9-16	3411640	**17**	volunteer$.tw.	179955
18	exp animals/ not humans.sh.	4051544	**18**	Crossover Procedure.sh.	38665

19	case report/	1681461	**19**	Double-blind Procedure.sh.	120596
20	letter/	827689	**20**	Randomized Controlled Trial.sh.	360301
21	historical article/	299778	**21**	Single-blind Procedure.sh.	18356
22	or/19-21	2629054	**22**	or/9-22	1407588
23	and/3,8,17	8167	**23**	animals/ not humans/	1408288
24	23 not 18	7890	**24**	22 not 23	1360886
25	24 not 22	7492	**25**	and/3,8,24	6644
26	limit 25 to yr="2011-current"	1897	**26**	case report/	1990514
27	remove duplicates from 28	1715	**27**	25 not 26	6572
28	eurointervention.jn.	1547	**28**	limit 27 to yr="2011-current"	2046
29	and/25,28	191	**29**	remove duplicates from 28	2006
30	limit 29 to yr="2002-2010"	101	**30**	(eurointervention or "eurointervention journal of europcr in collaboration with the working group on interventional cardiology of the european society of cardiology").jn.	2962
31	or/27,30	1816	**31**	and/27,30	316
32	Remove duplicates from 31	**1814**	**32**	31 not 28	134
			33	or/29,32	2140
				remove duplicates from 33	**2106**

* The Top-up aimed to retrieve citations with publication dates from 2011 to current, the time window that is incompletely covered by CENTRAL. In addition, a top-up search in the journal EuroIntervention was performed, as citations from this journal are typically missing in CENTRAL.

† Top-up search performed at 14 October 2013, using the following databases in OvidSP: Ovid MEDLINE(R) 1946 to October Week 1 2013; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 01, 2013; Ovid MEDLINE(R) Daily Update October 01, 2013.

‡ Top-up search performed at 14 October 2013, using the following database in OvidSP: EMBASE 1974 to 2013 October 11.