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SPECIAL ARTICLE

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

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The evaluation for European Union market approval of coronary stents falls under the Medical Device Directive that was adopted in 1993. Specific requirements for the assessment of coronary stents are laid out in supplementary advisory documents. In response to a call by the European Commission to make recommendations for a revision of the advisory document on the evaluation of coronary stents (*Appendix* 1 of MEDDEV 2.7.1), the European Society of Cardiology (ESC) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) established a Task Force to develop an expert advisory report. As basis for its report, the ESC-EAPCI Task Force reviewed existing processes, established a comprehensive list of all coronary drug-eluting stents that have received a CE mark to date, and undertook a systematic review of the literature of all published randomized clinical trials evaluating clinical and angiographic outcomes of coronary artery stents between 2002 and 2013. Based on these data, the TF provided recommendations to inform a new regulatory process for coronary stents. The main recommendations of the task force include implementation of a standardized non-clinical assessment of stents and a novel clinical evaluation pathway for market approval. The two-stage clinical evaluation plan includes recommendation for an initial pre-market trial with objective performance criteria (OPC) benchmarking using invasive imaging follow-up leading to conditional CE-mark approval and a subsequent mandatory, large-scale randomized trial with clinical endpoint evaluation leading to unconditional CE-mark. The data analysis from the systematic review of the Task Force may provide a basis for determination of OPC for use in future studies. This paper represents an executive summary of the Task Force's report.

Keywords Coronary stents • Drug-eluting stents • Bioresorbable stents • Coronary artery disease • Percutaneous coronary interventions

Background

In 2013, the European Society of Cardiology (ESC) was asked by the European Commission to make recommendations for a revision of the European Union (EU) medical device advisory document on the evaluation of coronary stents (*Appendix* 1 of MEDDEV 2.7.1)—the only device-specific standard that exists.[1] The ESC delegated the

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task to the European Association of Percutaneous Cardiovascular Interventions (EAPCI), which established a Task Force to develop an expert advisory report. As basis for its report, the ESC-EAPCI Task Force reviewed existing processes, established a comprehensive list of all drug-eluting coronary stents (DES) that have received a CE mark to date, undertook a systematic review of the literature of all published randomized clinical trials evaluating coronary artery stents between 2002 and 2013, and provided recommendations for a new regulatory process for coronary stents. This paper represents an executive summary of the Task Force's report.

Existing legislation and approval processes

The evaluation for EU market approval of coronary stents falls under the Medical Device Directive 93/42/EEC1993[2] that was adopted in 1993. It has been amended by the 2007/47/EC directive[3] and compliance with the revised directive became mandatory in March 2010. Devices are assigned to four groups according to risk to patient and/or user (I/IIa/IIb/III).[4] Stents are in class III and therefore require 'explicit prior authorization with regard to conformity'. Devices considered to meet the essential requirements must bear the CE mark of conformity when they are placed on the market. Specific requirements for the assessment of coronary stents are laid out in advisory documents including the EMEA/CHMP/EWP/110540/2007 document[5] and *Appendix* 1 of MEDDEV 2.7.1.[6]

The regulation of coronary stents and medical devices in general is the responsibility of each individual EU member state. The authorities responsible for this are known as competent authorities (CA). Competent authorities typically have responsibility for oversight of both drugs and devices in each member state and most have a Medical Device Unit, which specializes in the evaluation of these products. Competent authorities also receive reports of device incidents and oversee that appropriate action is taken by the manufacturer. Notified bodies (NBs) are third party bodies that can carry out a conformity assessment laid down in the relevant European standards. They are designated by Member States of the European Economic Area as well as by other countries (e.g. Switzerland or Turkey) having signed a specific agreement with the EU. The tasks of the NB include product certification, factory production control certification, and determination of the product-type on the basis of type testing.

Obtaining CE mark

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 current approval process for medical devices is illustrated in *Figure 1*. To acquire coronary stent approval, the manufacturer has to employ an NB. The duty of NBs is to review a technical dossier provided by the manufacturer, to test samples of the device as

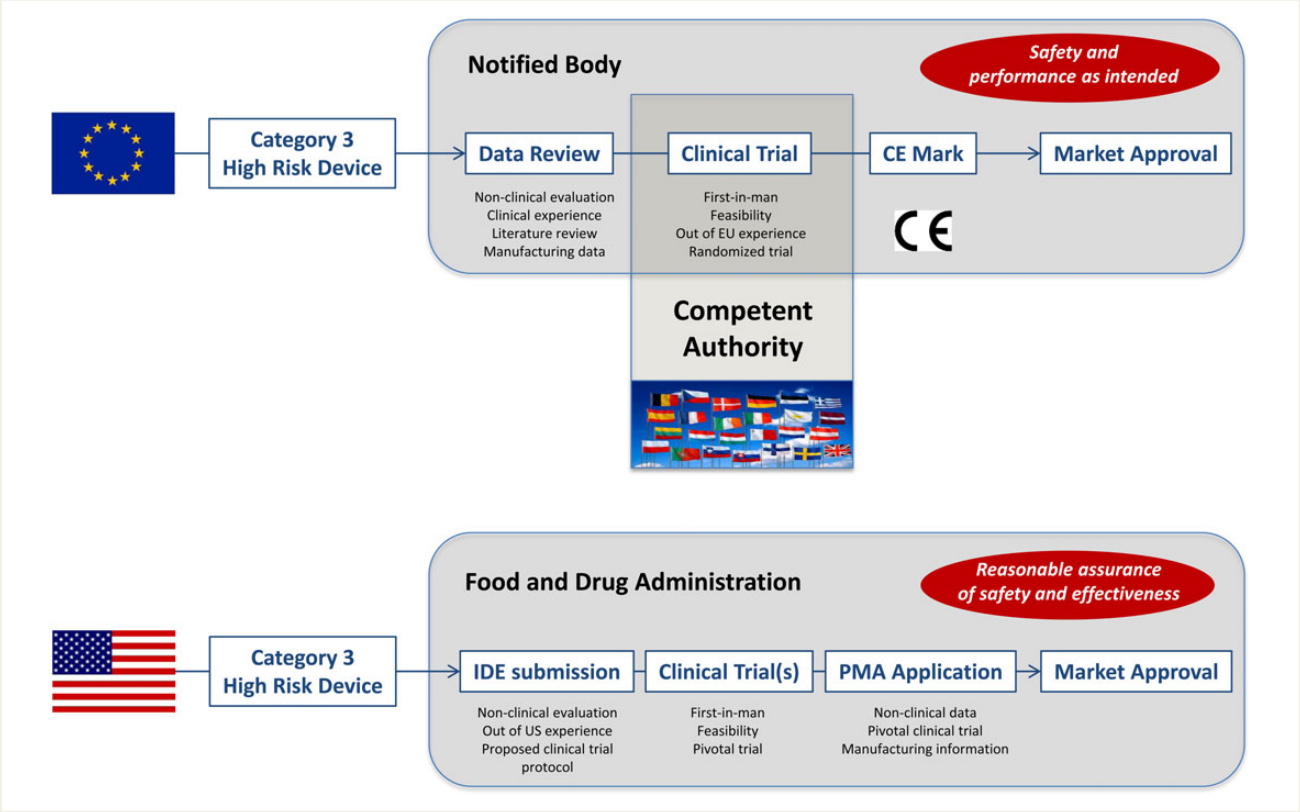

Figure 1 Summary of coronary stent approval pathways in Europe and in the United States. The pathway of approval related to coronary stents and major prerequisites to be fulfilled at various time points in Europe (top) and United States (bottom). IDE, Investigational Device Exemption; PMA, pre-market approval; OUS, out of United States.

required, and to evaluate the evidence presented in relation to non-clinical and clinical assessment. For class III devices, the manufacturer must conduct some clinical trials, but it is not compulsory that these are randomized trials. If the tests are satisfactory, then a certificate is issued and the CE mark can be affixed to the device.

Comparison with United States regulatory system

In the USA, market approval is the responsibility of the Food and Drug Administration (FDA). Coronary stents are in the highest risk class III and approval follows the regulatory pathway of pre-market approval (PMA) application. 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 USA, FDA approval of an Investigational Device Exemption must be obtained. The process is illustrated in *Figure 1*. Some concern exists that the present approval process is overly long and results in delay or denial of availability of clinically valuable devices to patients. The difficulty in finding balance between ensuring access to novel devices for unmet clinical needs while reducing risks associated with the early market approval of new devices has been recently articulated in discussions of the FDA on innovation and early feasibility studies.[7–10]

More detailed comparison of market approval in Europe and in the USA is presented elsewhere[4]; a summary is provided in *Table 1*.

Current issues regarding device approval in Europe

The European process for device regulation is usually regarded as being less onerous than the processes in some other jurisdictions.[4,11] This has advantages for patients in terms of timely access to important device innovations.[12] However, some concerns have been expressed regarding the thoroughness of evaluation of devices. For example, regulatory approval processes did not detect the small increased risk of very late stent thrombosis with the first-generation DES (though neither did US processes). At the same time, the current approval process for medical devices and clinical trials in Europe is fragmented and requires considerable improvement. The obstacles for approval of coronary stents can be classified within two major categories: (i) obstacles related to the complexity of the approval process per se and (ii) 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 a collaboration involving CA and NB (*Figure 1*). While issuing of CE marking is controlled by NBs, the regulation of clinical trials is performed by CAs. Each Member State has its own CA and a variable number of NBs (ranging from none to numerous). All of these agencies have varying application procedures and requirements.

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] A number of obstacles in the conduct of randomized clinical trials were highlighted by members of the Sensible Guidelines Group.[14] Thus, the initiation process to conduct a clinical trial requiring approval from multiple different entities including all CAs of participating EU countries as well as 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 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 individual cases instead of the more effective review of safety data by independent data and safety monitoring committees.

Table 1 Market approval procedures in Europe and the United States of America

	EU	USA	Comment
Oversight of pre-market approval investigations	National competent authorities and local ethics committees	FDA IDE	Time to approval for clinical studies tends to be faster in the EU
Market approval granting body	NB	FDA	NBs are mostly private companies; Ca. 80% of FDA funding is public, 20% is derived from user fees.
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	Role of post-market evaluation increasing in both systems
Transparency	Data not publically accessible; NB decisions and EUDAMED not accessible	Summary data published post-PMA; MAUDE registry publically accessible	More transparency in FDA process on review, recalls, and decisions
Reimbursement	National/regional commissioning with variable requirements	CMS clearance and code	Single market entry in USA 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; IDE, investigational device exemption; PMA, pre-market approval.

Systematic review of CE-marked coronary stents

To inform the report of the Task Force, a systematic review was performed to summarize available evidence of randomized clinical trials on CE-marked coronary 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 Supplementary material online, *Table S1*).

We restricted consideration to stents with published evidence of at least 1000 patients included in randomized clinical trials. 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. 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. Bioresorbable coronary stents were not represented in the review due to absence of published evidence meeting the inclusion criteria at the time of the review.

Table 2 Systematic review results—clinical outcomes in coronary stent trials with primary endpoint assessment at 9–12 months

	No. of contributing patients/trials	Outcomes at 9–12 months Median (IQR 25–75%) per 100 person-years
All-cause death (%)		
BMS	7011/21	2.29 (1.64–3.79)
DES	63 535/75	1.67 (0.99–2.59)
Early DES	31 937/63	1.64 (0.94–2.76)
New DES	31 598/37	1.92 (1.05–2.54)
FDA approved new DES	20 835/27	1.88 (1.01–2.47)
Cardiac death (%)		
BMS	5891/15	1.57 (0.88–2.81)
DES	59 334/59	1.00 (0.53–1.69)
Early DES	29 149/48	0.98 (0.50–1.83)
New DES	30 185/32	1.00 (0.65–1.63)
FDA approved new DES	20 135/25	0.99 (0.58–1.39)
Myocardial infarction (%)		
BMS	6315/19	3.29 (1.97–4.31)
DES	62 347/71	2.88 (1.41–4.57)
Early DES	30 976/59	2.88 (1.39–4.59)
New DES	31 371/36	2.89 (1.45–4.21)
FDA approved new DES	20 833/27	2.78 (1.33–4.26)
Target lesion revascularization (%)		
BMS	5557/17	12.32 (7.44–13.79)
DES	57 595/67	4.00 (2.05–6.40)
Early DES	26 729/56	4.34 (2.40–7.11)
New DES	30 866/35	2.91 (1.67–5.94)
FDA approved new DES	20 436/26	3.01 (1.75–4.72)
Definite stent thrombosis (%)		
BMS	6399/19	1.08 (0.57–1.94)
DES	54 393/58	0.61 (0.37–0.99)
Early DES	24 221/46	0.74 (0.45–1.19)
New DES	30 172/31	0.47 (0.28–0.72)
FDA approved new DES	19 634/22	0.43 (0.28–0.58)

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

Summary of results of systematic review

A summary of the search strategy and results is shown in Supplementary material online, *Figure S1*. A total of 158 randomized clinical trials were included (see Supplementary material online, *Table S2*). Summary characteristics of the identified trials are provided in Supplementary material online, *Table S3*. The median time of planned primary clinical outcome assessment was 12 months (IQR 9–12 months); the median time of planned angiographic surveillance was 8 months (IQR 6–9 months). Clinical and angiographic outcomes according to class of stent are reported in *Tables 2* and *3*, respectively.

Table 3 Systematic review results—angiographic follow-up outcomes in coronary stent trials

	No. of contributing patients/trials	Median (IQR 25–75%)
In-stent late lumen loss (mm)		
BMS	5659/42	0.90 (0.70–1.01)
DES	31 903/108	0.25 (0.14–0.44)
Early DES	19 467/94	0.30 (0.16–0.45)
New DES	9698/34	0.18 (0.13–0.25)
FDA approved new DES	5051/24	0.16 (0.13–0.22)
In-segment percentual diameter stenosis (%)		
BMS	5403/37	40.90 (36.80–44.40)
DES	29 713/100	24.71 (20.90–30.45)
Early DES	19 969/88	25.37 (20.70–30.45)
New DES	7355/31	23.15 (21.36–28.15)
FDA approved new DES	4256/22	22.75 (18.80–24.10)

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

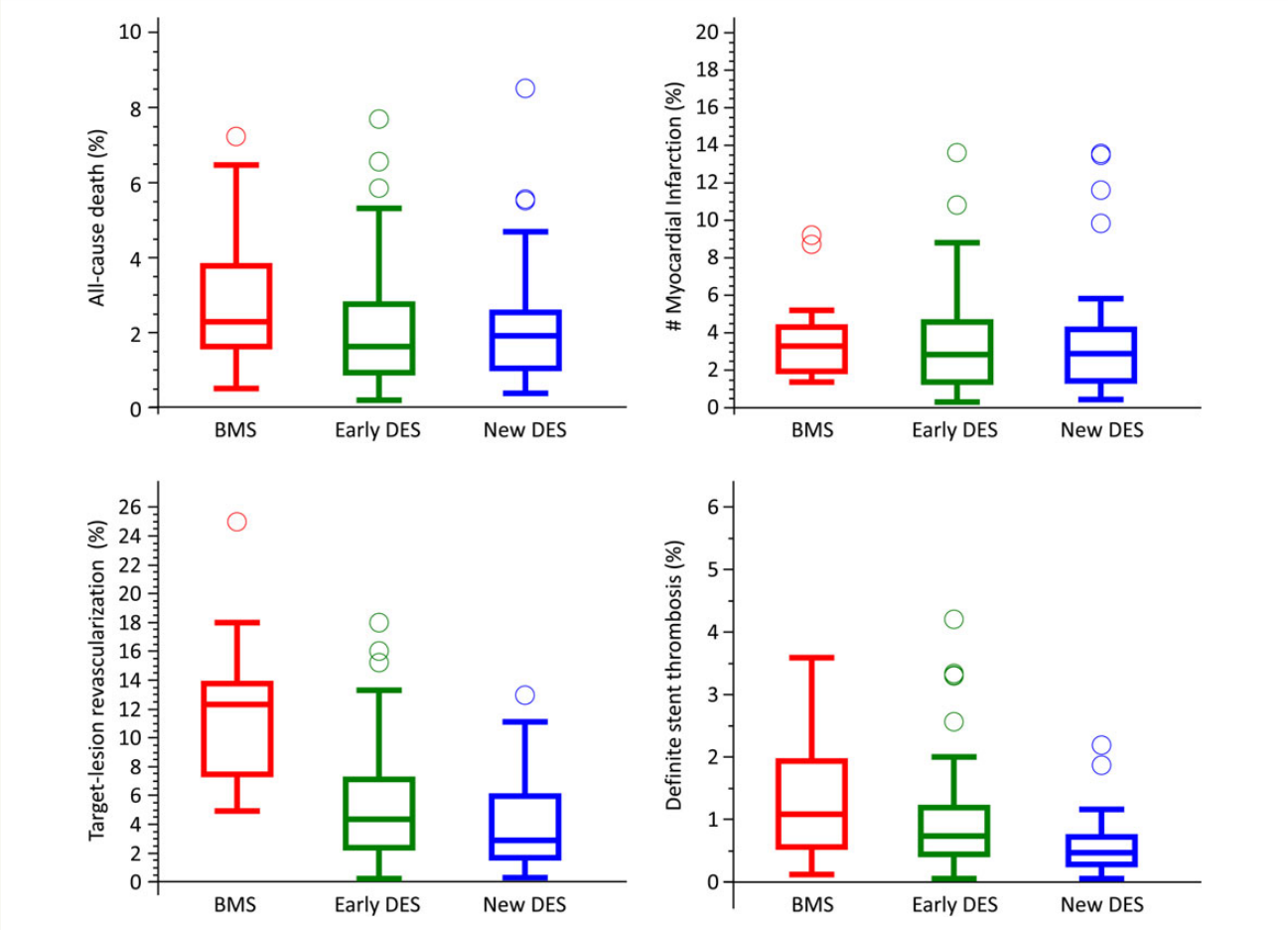

Figure 2 Systematic review results: clinical outcomes at 9–12 months—median rates per 100 person-years. Median rates and interquartile range per 100 person-year for the clinical endpoints all-cause death, myocardial infarction, target-lesion revascularization, and definite stent thrombosis. BMS, bare metal stents; DES, drug-eluting stents.

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 2 shows 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 3* shows 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.

Risk analysis in relation to coronary stents

Specific issues in relation to risk analysis of coronary stents are discussed in the Supplementary material online, Appendix and *Table S4*. Selected examples of coronary stent failures are shown in the Supplementary material online, *Table S5*.

Evaluation plan for coronary stents

Intended use and claims

In terms of medical device approval, a claim is a statement of treatment benefit. The intended use should be linked with the outcome claim. The objectives of the clinical trial should be to demonstrate

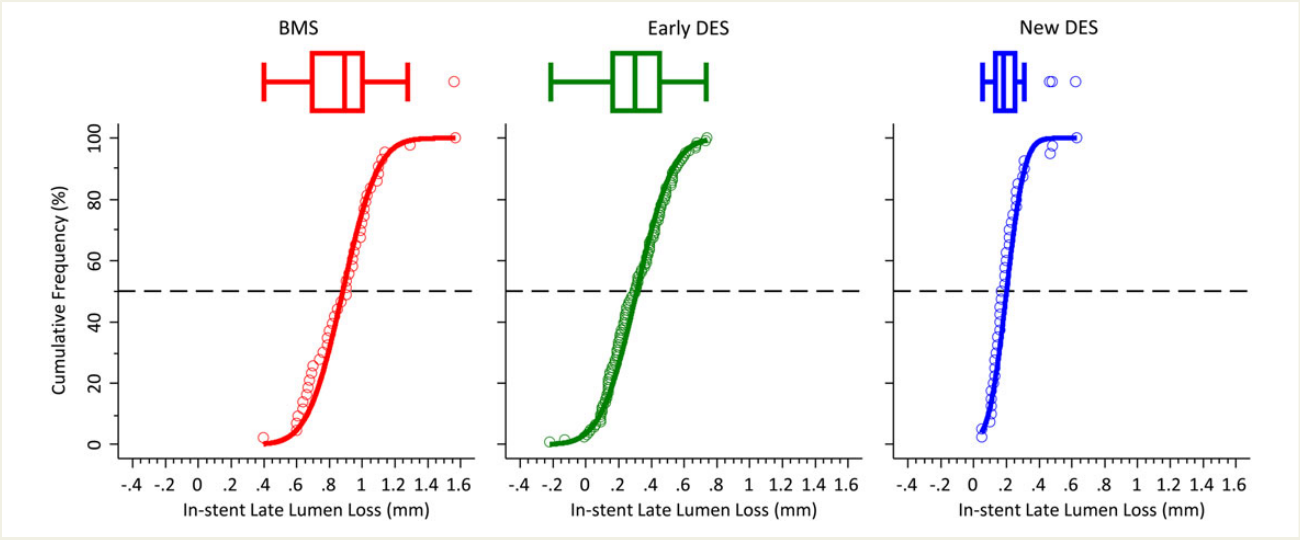

Figure 3 Systematic review results: median, interquartile range and cumulative frequency of in-stent late lumen loss. BMS, bare metal stents; DES, drug-eluting stents.

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

Typically, claims are tested by evaluation of clinical endpoints. These endpoint are discussed in detail below. However, patient-reported outcomes (PROs) may also be used to assess treatment benefit. A 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. The FDA has produced a detailed guidance on the use of PRO to make a claim and obtain product labelling.[15] The Task Force recommends that 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. However, there are certain challenges and requirements to accomplish PRO-based labelling: PROs are useful when device is used for symptomatic benefit but not applicable when it is used to achieve prognostic benefit. If PRO is to be used as trial outcome, blinding and randomization are important to avoid bias and placebo effect.

Non-clinical assessment

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 legislation for medical devices should be to ensure uniformity and transparency of non-clinical investigation in order to ensure device safety. In this respect, non-clinical studies are vital precursors to clinical investigation. The Task Force has formulated recommended 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 Good Laboratory Practice (GLP) standards is provided in *Table 4*. 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.

Bare metal stents

In general, 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 (see Supplementary material online, *Appendix*). Bench testing should be performed covering the full range of device sizes and designs, and the sample size per each device size should be justified.

Metallic drug-eluting stents

Non-clinical tests to mitigate risks associated with metallic DES include bench, biocompatibility, and *in vivo* studies as well as the assessment of the medicinal substance. DES are comprised of a metallic stent backbone, the permanent or bioresorbable coating (drug/carrier), and the delivery system. For the stent backbone component, the bench testing should be performed in three categories as described above. Additional or repeat testing may be 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 should be assessed and all associated risks should be considered when planning bench testing for non-resorbable DES.

The non-clinical evaluation of the medicinal substance on DES should include assessment of the non-clinical pharmacology and toxicology, clinical pharmacology (evaluation of pharmacokinetics), drug-release kinetics, and Chemistry Manufacturing Controls for the medicinal substance and for the finished product.

The drug carriers on DES are generally polymeric in nature. The recommended bench test requirements for the carriers include

Table 4 Checklist for non-clinical studies performed according to Good Laboratory Practice 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—Non-clinical and Clinical Studies (March 2008) • FDA Coronary Drug-Eluting Stents: Companion Document—Non-clinical 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 ◦ 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	• 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—Non-clinical and Clinical Studies (March 2008) • FDA Coronary Drug-Eluting Stents: Companion Document—Non-clinical and Clinical Studies (March 2008) • FDA Guidance for Industry and FDA Staff: General Considerations for Animal Studies for Cardiovascular Devices (2010) • Tearney et al.[24]
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—Non-clinical and Clinical Studies (March 2008) • FDA Coronary Drug-Eluting Stents: Companion Document—Non-clinical 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.

evaluation of the coating characteristics (i.e. chemistry, thickness and uniformity, adhesion to stent substrate), coating integrity (acute and chronic), particulate assessment, coating stability, and degradation profile (if the carrier is biodegradable).

Bioresorbable stents

Some of the risks associated with bioresorbable stents can be identified based on both non-clinical and clinical experiences from currently marketed devices as well as those that are under investigational use.

The Task Force recommends that bench testing of the biodegradable stent backbone should include two components: (i) characterization of the finished product and (ii) mechanical testing. Mechanical testing should follow the testing of metallic stents. However, use of a 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 may impact all aspects of product evaluation such as type of testing and timing of assessments. The duration of the accelerated fatigue testing should be determined through time of complete tissue coverage as determined by *in vivo* degradation studies. Particulate testing should be performed through time of significant mass loss of the polymer.

The biocompatibility testing for all devices 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 for DES (such as the extraction conditions and exposure times) and separate biocompatibility testing may be needed on degradation products for stents with biodegradable components.

In vivo testing of coronary stents

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.[16] Comparative studies are encouraged to appropriately reflect safety and biological responses. As a general rule, pre-clinical testing should be performed within the intended vascular territory.

The normolipidemic porcine coronary artery model is the most frequently used and widely accepted animal model to study the outcome of coronary stents.[16] 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 (targeted device-to-artery ratio should be between 1.0 and 1.2). In addition to the primary assessment of safety aspects, a general appreciation of efficacy should be reflected in pre-clinical study design.[17]

The Task Force recommends that for reasons of enhanced internal validity of data pre-clinical animal studies for regulatory approval should be performed in designated pre-clinical animal facilities with GLP certification. Study design must include appropriate controls to appreciate treatment effects especially with regards to safety and biocompatibility. 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. 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 and should cover complete resorption as determined by histopathology. 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.

Clinical imaging and functional assessment

The Task Force recommends that angiographic surveillance remains the imaging modality of choice for the evaluation of coronary stents. Offline quantitative coronary analysis in a centralized core laboratory with blinded outcome assessors in case of comparative studies is mandatory. The principal angiographic endpoints recommended by the Task Force are listed in Supplementary material online, *Table S6*. 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 $\geq$ 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.[18–20] Their use permits comprehensive analysis of device performance with benchmarking against a wealth of previously published data (see *Table 3* and *Figure 3*). The Task Force recommends that surveillance for the determination of angiographic endpoints be undertaken at 6–9 months after stent implantation, a time point which permits benchmarking of data against the majority of existing datasets, though it should be recognized that late loss after DES seems to be an on-going dynamic process at least out to 2–5 years.[21,22] In studies with primary clinical endpoint and angiographic substudies, angiographic follow-up is delayed until after assessment of the primary clinical endpoint, typically beyond 12 months.

Intra-coronary imaging can provide useful supplementary information. The principal intravascular ultrasound (IVUS) imaging endpoints recommended by the Task Force are outlined in Supplementary material online, *Table S6*.[23] An important limitation of IVUS is that although it can directly visualize neointimal tissue within the stented segment, limited axial resolution precludes determination of neointimal coverage of individual stent struts at follow-up. This issue is resolved by optical coherence tomography (OCT), which allows not only accurate ascertainment of information relating to morphometric stent performance (see Supplementary material online, *Table S6*)[24] but also assessment of vascular healing after stenting. The high resolution of OCT 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.[24] In addition, its high resolution facilitates detailed characterization of neointimal tissue as well as processes such as neoatherosclerosis at a tissue level.[25] However, thus far histopathological correlation data remain scant and the clinical implications of OCT acquired datasets are unclear.

Rapid advances in computer tomography (CT) coronary angiography technology have significantly enhanced the diagnostic

accuracy of this imaging modality. Its use in the assessment of stent performance and of calcified vessels with remains limited due to blooming artefacts.[26] Computer tomography angiography for the assessment of bioresorbable stents is promising.[27]

Convincing data to support the use of FFR for the evaluation of coronary stents during follow-up do not exist and due to the high efficacy of current devices systematic FFR evaluation is unlikely to permit clinically meaningful discrimination of stent performance. While various algorithms exist for the assessment of vasomotor function proximal and distal to the stented segment[28] the Task Force does not recommend routine use in the assessment of coronary stent devices.

Clinical assessment of coronary stents

Clinical trials of coronary stents may be designed as single-arm studies or randomized controlled trials (RCTs). Single-arm studies may be used in clinical evaluation to assess the general safety and efficacy of a novel device in isolation. Alternatively, they may be designed for prospective 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. Randomized controlled trials 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. In general, RCTs are the investigation of choice for comparative efficacy research though they are more expensive and time-consuming to conduct and the generalizability of results is sometimes unclear.

OPC studies represent an alternative to conventional RCTs. Studies with OPC comparison have been used for many years for certain medical devices such as prosthetic heart valves[29] and have more recently been used in study protocols designed for the approval of coronary stents by the FDA. However, the risks inherent in OPC comparison means that data endpoints must be highly standardized and that extensive datasets must exist to derive robust performance criteria. Coronary stenting is potentially suited to 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 which is larger than that acquired with any other medical devices.

Randomized controlled trial superiority trials hypothesize advantage of the study stent over the control stent. Non-inferiority trials test non-inferiority of the study stent vs. the control stent. 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.[30] For studies investigating novel coronary stents, the key elements of trial protocols recommended by the Task Force are shown in *Table 5*. The combined evaluation of new devices and systemic drugs, and their interaction, usually requires large post-market surveillance studies. Some groups have recently proposed to incorporate randomization within nationwide clinical registries, which may increase clinical relevance and applicability of trial results.[31]

In coronary stent trials, composite endpoints that capture events clearly related to the mechanism of the study device—device-oriented composite endpoints—are generally preferred.[32,33] The most commonly used is the composite of cardiac death, target vessel myocardial infarction, and target-lesion revascularization—sometimes termed target-lesion failure (TLF). This is the endpoint recommended by the Task Force for trials powered for clinical endpoints. However, composite endpoints that capture broader cardiovascular outcomes—patient-oriented composite endpoints—are also of interest. The most commonly used is the composite of all-cause death, any myocardial infarction, and any revascularization. This endpoint should also be reported. The individual safety and

Table 5 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 6 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 composite endpoint)
– All-cause death, any myocardial infarction, and any revascularization (patient-oriented composite endpoint)

The Task Force recommends clinical follow-up at a minimum of 30 days, 12 months, and 5 years after stent implantation.

efficacy endpoints recommended by the Task Force are listed in *Table 6*. Data collection should be monitored by an independent data monitor in a pre-specified proportion of cases. Clinical endpoints should be adjudicated by assessors blinded to the treatment received.

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. Events occurring within 30 days of the intervention are considered procedure related. 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 performed at 12 months. Thereafter, follow-up up to 5 years is performed in order to detect any late adverse event. The Task Force recommends follow-up at all three time points.

In terms of clinical investigation, the priority should be to facilitate advances and disruptive innovations that target unmet clinical needs. The Task Force identifies particular unmet needs for patients with diabetes, end-stage renal disease, extensive and diffuse multi-vessel coronary artery disease, and those with cardiac allograft vasculopathy, as well as subsets of lesions with vulnerable plaques, thrombus burden, bifurcation disease, in saphenous vein grafts or areas of coronary aneurysm, and chronic total occlusion.

Device iterations

The Task Force proposes to differentiate between the evaluation process for new devices as opposed to device iterations. We propose to define device iterations as changes to 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 non-clinical performance characteristics. 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 non-clinical performance characteristics but not necessarily clinical performance criteria.

Clinical development plan

The Task Force proposes a clinical development plan for the evaluation of novel coronary devices (both metallic DES and bioresorbable stents) in Europe. In developing this recommendation, the most important work of the Task Force is to balance the preservation of patient safety with the avoidance of unnecessary delays in the introduction of innovative technology for clinical use. The key steps in the process proposed by the Task Force are outlined in *Figure 4*.

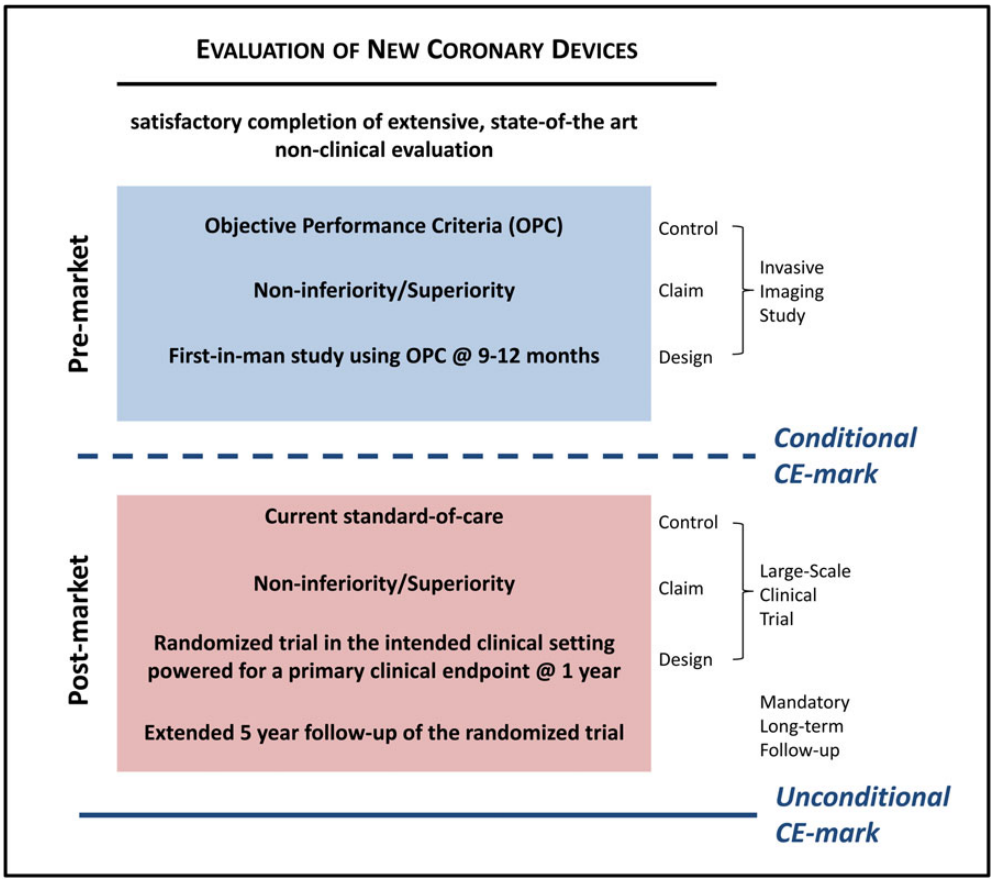

Figure 4 Proposed clinical development plan. Proposed clinical development plan from non-clinical evaluation to post-market surveillance. OPC, objective performance criteria.

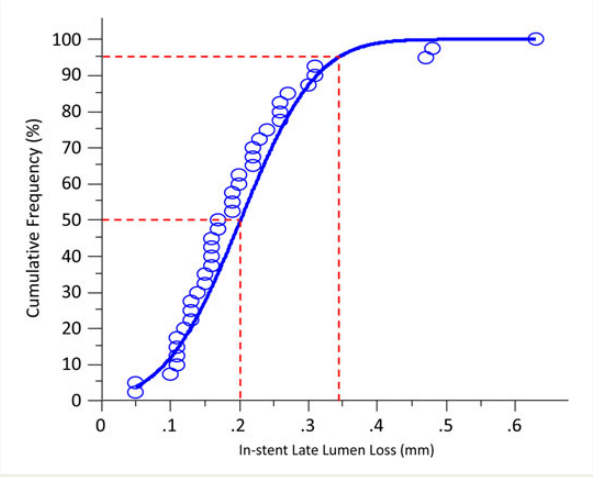

Figure 5 Nomogram for in-stent late lumen loss for new-generation DES suitable for use for the design of OPC study. Pooled estimate and corresponding between-trial variance were used to fit a cumulative distribution curve by stent group that could be used as a nomogram to derive OPC for future DES evaluated in pre-approval single-arm studies. The Task Force proposes use of the nomogram to derive mean late lumen loss (i.e. 0.20 mm) and upper the 95th percentile (i.e. 0.34 mm) to be used for sample size calculation of trials using OPC.

The device manufacturer proposes a clinical study based on a pre-specified claim of non-inferiority or potential benefit compared with OPC derived from the standard-of-care devices (currently new-generation DES as defined in the systematic review). The design for the PMA study will typically consist of a study with a pre-specified OPC control assessed at 9–12 months follow-up using invasive imaging and an imaging primary endpoint. If the pre-specified outcomes are fulfilled against the pre-specified OPC, the product may receive conditional CE-mark approval. In case, OPC for a specific intended use are lacking the Task Force recommends that an RCT should be done. Alternatively, a device manufacturer may prefer to conduct an RCT rather than use a pre-specified OPC. To derive an empirical basis for OPC for the angiographic endpoint in-stent late lumen loss, the Task Force performed a systematic review separately for BMS, early- and new-generation DES of trial arms with available angiographic data (*Figure 5*).

Following conditional CE-mark approval, the device manufacturer is mandated to initiate, conduct, and complete a compulsory randomized clinical trial powered for 1-year 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. Typically, it is estimated that using realistic assumptions and standard statistical approaches OPC studies would have a sample size of 150–300 patients. Post-market RCTs powered for clinical endpoint would typically have a sample size of 1500–3000 patients. If the novel device fulfils 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.

Additional recommendations of the Task Force can be summarized as follows:

(1) The life cycle of coronary stents is short due to rapid device iteration and innovation, which can make early-generation devices clinically obsolete in <5 years. The Task Force emphasizes that in PMA process should be as efficient as possible in order that timely access to improved devices for patients is maintained.

(2) 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.

(3) The Task Force has identified areas of unmet need for coronary stents and may particularly benefit from innovative technologies. The Task Force recognizes that under ideal circumstances devices should be categorized into conventional devices (alternative treatment with well-established standard-of-care available) and innovative devices (no or limited treatment with established standard-of-care available). However, this distinction may be difficult and in order to avoid ambiguity, the Task Force concludes that a uniform assessment pathway remains preferable.

(4) The Task Force acknowledges the critical role of post-marketing surveillance in 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.[34,35] The Task Force therefore highlights the importance of long-term follow-up in populations representative of routine clinical practice and proposes the concept of mandatory large-scale randomized trial with long-term follow-up after initial conditional market approval (see *Figure 4*).

(5) Trial evidence resulting in CE-approval as it relates to coronary artery stents shows great heterogeneity. Therefore, the 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 (i) contemporary coronary artery stents achieve a high and predictable clinical safety and efficacy and (ii) clinical and angiographic endpoints to evaluate the performance of coronary artery stents are well established.

For this reason, the Task Force proposes OPC evaluation of coronary artery stents during early clinical investigation.

(7) To improve transparency in relation to the conduct and reporting of clinical trials the Task Force proposes to implement the following mandatory processes:
   (a) systematic public registration for all clinical investigations leading to CE approval,
   (b) publication of decision-making process of NBs that lead to conditional and full CE approval of medical devices on a publicly accessible website,
   (c) publication of the results of all post-marketing surveillance studies initiated for full CE approval,
   (d) to create a central publically accessible database of all coronary stents with CE approval and related clinical trial evidence,

(8) Due to geographical variation in clinical trial data (e.g. disease incidence and patterns, treatment response, and trial conduct), the Task Force recommends to recruit a minimum of half of all patients in Europe for clinical trials with medical devices intended to support application for CE-mark approval.

(9) The instructions for use should provide clear guidance as to the appropriate indications and contra-indications for a particular device.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Appendix

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; Javier Escaned: Treasurer; George Sianos: Past Secretary; Robert Byrne: Co-Chair, Scientific Documents Committee)
- EuroPCR representative (William Wijns, Chairman)
- ESC Task Force Medical Devices (Stefan James, Stephan Windecker)
- ESC-EACTS Task Force on Myocardial Revascularization (Stephan Windecker: Co-Chairman; Members: Adnan Kastrati, Giulio Stefanini, Peter Jüni; William Wijns: past Co-Chairman)
- 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 European Heart Journal; Patrick Serruys: Editor-in-Chief EuroIntervention)
- CVPath non-profit organization, Gaithersburg, USA (Michael Joner)
- CardioMed Device Consultants, consultant to CVPath, former FDA reviewer (Semih Oktay)

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