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## Working Group Report

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# Recommendations on stent manufacture, implantation and utilization

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### Historical perspective

The neologism ‘stent’ has irrevocably entered the English medical vocabulary as a noun as well as a verb<sup>[1]</sup>. It allegedly dates back to the English dentists Charles T. Stent (1807–1885) and his sons Charles R. Stent (1845–1901) and Arthur H. Stent (1859–1900) who used to support poorly aligned teeth with a special apparatus<sup>[1]</sup>. Others have traced the word back to the 14th century. The first mention of the word stent in the (non-dentistry) medical literature can be found in a paper on reconstruction of the biliary duct in dogs in 1954<sup>[2]</sup>. Charles Dotter employed the term stent for vascular implants in 1983<sup>[3]</sup> when he presented the first clinical experience with a percutaneously implanted vascular endoprosthesis based on prior canine experiments in 1969<sup>[4]</sup>. As a further development to heat-expandable stents, Maass published animal data in 1983 and 1984 on mechanically self-expanding stents for use in peripheral arteries<sup>[5,6]</sup>. In 1985, a spring-loaded self-expanding stent was described by Gianturco’s group<sup>[7]</sup>, followed by the first balloon-expandable stent by Palmaz<sup>[8]</sup> and a self-expanding mesh-stent by Rousseau and Sigwart<sup>[9,10]</sup>.

In 1987 the first animal studies on coronary stenting were published<sup>[11,12]</sup>. The first human implantation using the self-expanding mesh-stent or Wallstent was carried out by Puel on 28 March 1986<sup>[13]</sup>. Its initial development had been hampered by several problems. First, the risk of subacute thrombotic coronary artery closure several days after the procedure emerged as a novel, stent-specific hazard prompting complex anticoagulation regimens, associated with increased bleeding and prolonged hospital stays<sup>[10,14–18]</sup>. Second, shortly after the clinical introduction of the stent, Medinvent (the Swiss firm producing the Wallstent) became part of the American Pfizer company. Pfizer had been beset by major difficulties with a heart valve of their subsidiary

Shiley, and thus proceeded with extreme caution in launching the stent because it was felt to be another implantable device potentially necessitating a later call-back campaign. Following the unavailability of the Wallstent, the Palmaz–Schatz<sup>[19,20]</sup>, the Gianturco–Roubin<sup>[21]</sup> and the Wiktor<sup>[22]</sup> stents developed concurrently, but were only available to selected centres under strict research regulations. Third, the limitation of stenting to acute and threatening occlusions after coronary angioplasty yielded early success and complication rates that were not always competitive with those of routine angioplasty<sup>[23–25]</sup>. Insufficient consideration was given to the fact that the stent much improved the otherwise dismal outcome of these patients, and randomized studies were lacking. Fourth, other new devices, such as the laser, rotational ablation, and directional atherectomy, frequently utilized in low-risk situations in contrast to the stent, appeared to many as more attractive as they did not require prolonged and enforced anticoagulation<sup>[26]</sup>.

The sobering accounts on the first roughly 100 patients with a coronary stent fraught with all the adverse risk factors enumerated above<sup>[14,27]</sup>, amplified by an explicit editorial<sup>[28]</sup>, all but extinguished the flickering flame of stent enthusiasm in 1991. It was not until several years later that the common error of looking at the stent as just another new device for coronary angioplasty was first challenged and then corrected by the results of well designed randomized trials<sup>[29,30]</sup>. These trials, initiated by Serruys and his colleagues from the Benestent group, proved that primary stent implantation in elective cases could reduce angiographic restenosis rates<sup>[29,30]</sup> and improve the patient’s clinical outcome<sup>[29,31]</sup>, as compared with balloon angioplasty. Eventually, following the lead of Colombo and others<sup>[32]</sup>, the implantation technique was improved by focusing on full expansion, adequate deployment of the stent using intravascular ultrasound<sup>[33–35]</sup>, and by the use of simplified and more effective anticoagulation protocols<sup>[36–40]</sup>.

Since then, the stent has gained ground at an incredible speed. In 1995 it was used in most coronary angioplasty procedures at leading centres and in 30–60% of all cases at other centres<sup>[41]</sup>. Over 20 stent

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manufacturers are now competing for the European market. Stents in a great variety of lengths, diameters, and other physical properties have found a place on the shelves of all active catheterization laboratories. Today, stents are considered indispensable in coronary angioplasty<sup>[42]</sup>, as much as balloons and digital imaging. As will be discussed hereafter, stents reduce the risk of abrupt vessel closure thereby enhancing the overall safety of percutaneous revascularization procedures. They also reduce restenosis in some subsets. Stents may therefore enlarge the indication spectrum for coronary angioplasty and include complex cases hitherto requiring coronary bypass surgery. Stents may even be of economic benefit provided they are sold at reasonable prices, employed prudently, and proven to be of long-term efficacy<sup>[43-45]</sup>.

### Objectives of these recommendations

The primary and legal context of these guidelines is the compulsory application of the 'Medical Devices Directives' of the EC from June 1998. Intracoronary stents fall into category III, the group of devices considered to be at the highest level in terms of risk of use<sup>[46,47]</sup>. As a group representative of the medical and scientific community, we want to express a consensus opinion about a number of regulatory issues, with the aim of promoting new developments and research in this area. At the same time, our intention is to protect patients and colleagues from hazards that could result from the premature or uncontrolled dissemination of unsafe devices.

The two sides of this issue are equally important. In the two last decades, we have enjoyed a period of 'freedom' in Europe that has permitted the development of anything new in invasive cardiology, starting with balloon angioplasty. We hope that European investigators will not be plagued with the administrative restrictions that have affected the research and clinical endeavours of our U.S. colleagues. However, before a stent can be released on the market for unrestricted use, a number of requirements should be met. These will take into account that the device will be permanently implanted on the surface of the beating heart.

From the industry's viewpoint, the major companies welcome the establishment of such guidelines, particularly in order to clarify liability issues, a major concern in cases of permanent implantation. The guidelines should also be helpful to the smaller companies, who are often developing innovative concepts. Lastly, these 'home-made' stents or 'clones' of commercially available stents should comply with our recommendations.

The following paragraphs describe the stents available for intracoronary use. The evaluation scheme for the manufacturing, quality control, and testing of coronary stents is summarized. Finally, we will describe the current, and attempt to anticipate the near future, indications for stent implantation.

There are a number of other important issues in relation to the utilization of coronary stents (i.e. require-

ments for training interventional cardiologists performing these procedures and the role of intravascular ultrasound guidance during implantation and deployment). Both issues have been addressed in detail in previously published guidelines<sup>[48,49]</sup>.

### Type of stents for coronary applications

Currently, stents are delivered through self-expansion or via balloon expansion. The most commonly encountered designs include tubular mesh, slotted tubes or coils. Different types of metal have been used, among which are stainless steel, tantalum, nitinol, cobalt alloy and platinum iridium. A list of some of the stents available for coronary implantation is given in Table 1 and a detailed description is provided elsewhere<sup>[50]</sup>.

It should be noted that there is a warning about rapid evolutionary changes. The implantation technique, the role of adjunctive therapies, and the devices themselves are undergoing continuous evolutionary change. This means that the differences between stents are such that results obtained with one type of design or metal cannot simply be extrapolated to others. However, minor changes in existing stents may not require comprehensive repeat evaluation, as delineated below, but if existing stents undergo continuous modification, it is possible that even minor changes may unintentionally adversely affect their effectiveness. Major modifications include the use of a different metal or a fundamental change in design. Copies of existing stents should be thoroughly evaluated. The use of coatings should be considered as a major modification. Whenever stents are used as a platform for local delivery of drugs or radiation, the specific effects of these agents should be evaluated separately prior to clinical investigation<sup>[51]</sup>.

### Proposal for an evaluation scheme of coronary stents

The overall goal is to 'protéger sans étouffer'. To balance these two apparently contradictory attitudes, a clear distinction should be made between devices that can be used without restriction vs stents that are still under evaluation. This applies equally to copies of existing stents.

To this end, we propose formalizing an evaluation scheme; this is similar to the four phases required for the introduction of a new drug:

- phase 1: in vitro testing
- phase 2: animal studies
- phase 3: clinical evaluation (restricted availability)
- phase 4: clinical application (unlimited availability and further trials)

#### *Phase 1: in vitro testing*

The industry is obviously responsible for this evaluation phase, but we feel it is necessary for clinicians using these

**Table 1** List of some stents currently proposed for coronary implantation in Europe

Stent	Company	Metal	Design	Expanded metallic surface (%)
<b>(A) Self-expanding stents</b>				
Angiomed	Bard	nitinol	wire braid	16–29%
Cardiocoil	In-stent Medtronic	nitinol	spiral coil	8–15%
Radius	Scimed	nitinol	slotted tube, zig-zag design	20%
Wallstent	Schneider	cobalt alloy, platinum core	wire mesh	± 15%
<b>(B) Balloon expandable stents</b>				
Act-one	ACT	nitinol	slotted tube	20–25%
Angiostent	Angiodynamics	platinum-iridium	sinusoidal single wire coil, longitudinal spine	9–12%
be-Stent	In-stent Medtronic	stainless steel	slotted tube, serpentine mesh, rotating junctions	11–18%
BioDiv Ysio	Biocompatibles	stainless steel	slotted tube, phosphoryl-choline coating	NA
Cordis	Cordis	tantalum	single helical coil	18%
Cross-flex	Cordis	stainless steel	single helical coil	15%
Crown	JJIS	stainless steel	slotted tube, sinusoidal slot	<20%
Freedom	Global Therapeutics	stainless steel	fishbone, single round wire	11–15%
Gianturco-Roubin II	Cook	stainless steel	flexible coil, single flat wire, longitudinal spine	15–20%
Jo-med	Devon	stainless steel	slotted tube, cellular mesh	NA
Microstent GFX	AVE	stainless steel	connected zig-zag wires, 2 mm long modules	8.5%
Multilink	Guidant-ACS	stainless steel	multiple rings	15%
NIR	Medinol-Scimed	stainless steel	Multicellular	14–19%
NIR Royal		gold plated		
Palmaz-Schatz	JJIS	stainless steel	slotted tube, spiral articulation	<20%
STS	De Scheerder	stainless steel	helical coil	5–15%
Tensum	Biotronik	silicon carbide coated tantalum	slotted tube, 2 articulations	13%
Wiktor-GX	Medtronic	tantalum	helical coil,	7–10%
Wiktor-i	Medtronic	tantalum	single wire	8–9.5%
X-Trode	Bard	stainless steel	connected round wires, longitudinal spine	16–19%

\*Several stents are available with heparin coating. Further technical details are available elsewhere<sup>[50]</sup>.

devices to understand and know in some detail about the testing requirements. The following section is largely taken, with permission, from the 'Guidance Document for Interventional Cardiology Devices' established by the Interventional Cardiology Devices Branch of the US Food and Drug Administration<sup>[52]</sup>.

In vitro studies of intravascular stents include both bench testing and non-human biological testing. The data generated during this phase of testing should be conducted according to a consistent and established protocol. The results of these tests should be reported in a statistically meaningful format, i.e. specifications of the number of samples, range of values, mean, standard deviation and lower tolerance limits at a 95% probability.

For any comparative test, a *P*-value (or similar measure) indicating the statistical significance of the comparison should be provided. Test samples must have undergone sterilization by the process to be used for production purposes and, where appropriate, subjected to the recommended maximum number of re-sterilization cycles using the worst-case method and/or conditions specified.

#### Specification conformance testing

The following tests should be conducted on clean and processed material samples, i.e. metal wire or any other material.

(a) *Material analysis.* Samples should be chemically analysed and impurities quantified to ppm accuracy. In addition, scanning electron microscopy testing should be performed to detect any evidence of surface contamination or impurities.

(b) *Mechanical properties.* Samples should be measured for tensile strength and elongation.

(c) *Corrosion.* Samples should be analysed for resistance to corrosion.

#### Stent integrity

The following tests should be conducted on finished, sterilized stents after deployment with the proposed delivery system, except where noted.

(a) *Stent free area percentage and dimensional changes.*

The percentage change of the free or open area and the decrease in the length, as a function of stent diameter, should be determined and a graphical representation of such submitted.

(b) *Stent uniformity testing.* The uniformity of the expanded stent should be determined by quantitative documentation after expansion in a tube and should be consistent with the labelled expanded diameter.

(c) *Radial (hoop) strength.* The change in stent diameter as a function of circumferential pressure should be determined. The pressure at which deformation is no longer completely reversible should be recorded.

(d) *Fatigue testing.* An in-depth analysis of the stent's fatigue resistance is required to assure that the arterial/venous implant conditions to which the stent will be subjected will not result in fatigue and corrosion despite millions of cycles of stress for 10 years equivalent. The following data are required:

- (1) A finite element or other stress analysis that identifies the peak stresses in the stent when subjected to a worst-case physiological load. The amount of residual stress must be determined and accounted for when calculating safety factors. This analysis should demonstrate that fatigue failure will not occur during the implant life of the stent. The use of finished, sterilized stents is not necessary for finite element analysis.
- (2) Accelerated in vitro testing of approximately 10 years equivalent real time should be conducted on a statistically significant sample of stents expanded to their intended diameters and dynamically cycled over simulated vessel conditions at 37 °C, which must include a standardized bending process. A complete description of the test protocol and sample preparation used in this study should be provided.

(e) *Stent recoil.* The amount of elastic recoil (spring-back) for each size stent should be quantified and correlated to the recommended placement (sizing) procedure.

(f) *Magnetic resonance imaging.* It should be determined whether the stent will be subject to displacement or cause artifacts with magnetic resonance imaging due to distortion of the magnetic field.

(g) *Stent expansion.* It should be determined whether the plastic deformation experienced by the stent in going from its initial to final position could give rise to crack initiation. An examination of expanded stents, using the proposed delivery system, should be performed under an appropriate magnification. In addition, the smallest flaw size (length, width, and depth) that can be detected by quality control inspectors on the surface of the stent, should be specified.

(h) *Dimensional verification.* The stent should be measured and visually inspected to document that no dimensional specifications deviate from the design specifications.

(i) *Stent thrombogenicity.* Stent thrombogenicity should be evaluated in a closed loop system. Comparison with an approved stent should be performed.

(j) *Stent surface characteristics.* Surface smoothness should be evaluated using scanning electron microscopy

and laser tomography. This point is of particular importance as sharp edges, uneven surfaces or irregular welding points may cause balloon rupture at inflation.

#### *Stent/catheter system testing*

Testing is needed to demonstrate that the delivery catheter can safely and reliably deliver the stent to the intended location and that the stent is not adversely affected by the catheter. Unless otherwise noted, all testing should be conducted on complete sterilized assemblies with stents mounted and after the device has been soaked in a 37 °C saline bath.

(a) *Maximum pressure.* Maximum pressure tests should be conducted on balloon/stents of each size and length. The results must show statistically that, with 95% confidence, 99.9% of the catheters will not experience balloon, shaft, proximal adaptation, or proximal/distal seal loss of integrity at or below the maximum recommended pressure, i.e. the pressure required to expand the stent to its labelled diameter.

(b) *Stent diameter vs balloon inflation pressure.* This test should be conducted on balloons/stents of each diameter and the stent diameter vs inflation pressure should be plotted. This graph, or a tabular representation, should be provided in the Instructions for Use and/or on the package labelling.

(c) *Bond strength.* Test the bond strength at locations where adhesives or other junction bonding methods are used for bonding between parts of the catheter.

(d) *Diameter and profile.* Determine the diameter of the catheter shaft, the profile of the balloons, and inflated diameter of the balloons to ensure that the actual diameter matches the labelled diameter. Stent mounting is not required.

(e) *Balloon deflatability.* Show that the balloon can be completely deflated by the recommended procedure following stent expansion, when it is in an environment simulating a stenosed vessel. Observe and describe any interference with balloon deflation. In addition, observe and describe any interference in withdrawing the deflated balloon from the deployed stent.

(f) *Balloon inflation and deflation time.* Show that inflation and deflation of the balloon, using the recommended procedure, can be accomplished within a specified time.

(g) *Tip pulling and torqueing.* Show that the force required to break the joints and/or materials at the distal end of the catheter is sufficiently strong to assure the integrity of the tip during pulling, pushing, or torqueing manoeuvres.

(h) *Stent crimping.* If the stent is not provided pre-mounted on the delivery catheter, testing must be

performed to show the functionality of all crimping devices and that the crimping procedure will not damage the stent, balloon or catheter.

(i) *Crossing profile.* Determine the crossing profile of the stent/delivery system and discuss its clinical acceptability.

(j) *Compatibility.* Indicate the minimum outer and internal diameter of the guiding catheters and the maximum guide wire size that is applicable.

### Phase 2: animal testing

Major problems when using coronary stents are:

- (1) inappropriate delivery of the stent;
- (2) subacute stent closure due, in part, to the thrombogenicity of the stent;
- (3) neointimal hyperplasia resulting in stent restenosis.

The purpose of animal studies is to evaluate the feasibility and safety of stent delivery, the performance of the delivery catheter, the early and late patency rates of the stent, and the biological reaction of the vessel.

The model that we suggest is the porcine coronary model<sup>[53,54]</sup>. This model accurately mimics the proliferation component of human restenosis and is practical as well as inexpensive. A minimum of 50 stents should be evaluated. The vessels selected for testing must have diameters similar to those proposed for stent placement in humans. Preferably, the selection of stent size and stent deployment should be performed under guidance of quantitative coronary angiography or intravascular ultrasound so as to avoid excessive overstretch. The smallest and largest diameter stents must be included in the animal studies.

The majority of stents must remain implanted for a minimum of 4 weeks and some stents should be explanted at periodic intervals in order to evaluate thrombus formation and to characterize the re-endothelization process completely. A minimum of five animals should be followed for 6 months or longer to evaluate potential late complications. For this purpose, juvenile mini-pigs are preferred to avoid excessive growth of the animals during the course of the study.

The testing protocol(s), test results and study conclusions should be fully described in order that an independent evaluation of the conclusions can be made. In addition to documenting all complications occurring during the procedure and follow-up, the following is required.

#### Study parameters

- (a) Provide a clear description of the pre-stenting vessel characteristics, i.e. lumen diameter as obtained from arteriography pre-, post-stenting and at follow-up.
- (b) Describe the anti-coagulation therapy used in the animal studies, with respect to its similarity to that proposed in the clinical situation.

- (c) Document the exact specifications of the stents used, i.e. unexpanded diameter, length, expanded diameter, and inflation pressure.
- (d) Document the use of multiple stents at one lesion location.

#### Performance of the stent/delivery system

(a) *Preparation.* The ease by which the device can be prepared for use.

(b) *Introduction.* The ability of the device to be loaded onto the guidewire or into a guiding catheter.

(c) *Pushability.* The ability of the system to transmit sufficient, even force proximally, allowing for equal and smooth movement distally.

(d) *Trackability.* The ability of the system to advance distally over a guidewire, following the guidewire tip, along the path of the vessel, including in narrow, tortuous vessels.

(e) *Flexibility.* The ability of the stent/delivery system to bend in order to accommodate a turn or angle it is required to negotiate, and the flexibility of the stent to conform with the vessel after the stent is deployed.

(f) *Radiopacity.* The visibility of the stent and delivery system under fluoroscopy.

(g) *Inspection.* A post-evaluation inspection to document any evidence of damage to the delivery system.

(h) *Accessories.* A description of the performance of all accessories recommended in the labelling, such as guiding catheter, haemostasis valves, sheaths, etc.

#### Angiographic, haemodynamic and histological results

(a) *Angiographic results.* Determine flow characteristics in the stented vessel immediately following stent deployment and immediately prior to explantation. In addition, note the angiographic presence and amount of acute thrombus.

(b) *Haemodynamic data.* Determine if ECG or blood pressure changes were noted during the implantation period. Document any cases of distal embolization.

(c) *Histological results.* (1) Measure the neointimal thickness at each follow-up throughout the stented length, including at stent/artery junctures. (2) Document any occurrences of intravascular trauma induced by stent placement in the vessel of interest. (3) Provide a pathology report including gross findings and microscopic studies involving both conventional and scanning electron microscopic techniques. The explanted vessel should be evaluated for outer diameter enlargement, lumen narrowing, filling defects, patency of side branches, protrusions of the stent into the vessel lumen, and medial thinning. (4) Conduct a detailed examination of explanted stents to document integrity.

### Phase 3: clinical evaluation under restricted availability

Each new intracoronary stent, including new designs of previously tested stents or known stents undergoing major modifications, have to be carefully evaluated in patients and the following data must be recorded *before the stents are offered for sale*. These data should be obtained prospectively from a multicentre, international study with data monitoring by an independent core laboratory. Experienced investigators should perform these initial evaluation studies. A minimum of 100 patients should be included and clinical and angiographic follow-up data obtained at 6 months. These results should be compared with those previously obtained using other stents evaluated in similar patient and lesion subsets.

1 <i>Pre-procedural data</i>	Gender and age.
2 <i>Procedural data</i>	
Stented vessel	Segment number (according to the AHA classification). Complex lesions should not be included in this initial evaluation.
Stent indication	Unsatisfactory result after balloon angioplasty attempt, restenotic lesion, elective implantation.
Implantation technique	Maximum implantation pressure, access site.
Procedural result	Angiographic success defined as a residual stenosis <30% in diameter.
Technical complications	Stent loss (removed or lost into blood circulation), ectopic implantation.
Clinical outcome	All major adverse cardiac events (MACE) occurring during hospital stay should be carefully recorded, as well as the need for femoral repair or blood transfusion.
Quantitative coronary angiography	Performed before and after stenting by an independent core laboratory.

### 3 *Antithrombotic protocol*

The dosage and duration of drug therapy is specified:

- aspirin
- ticlopidine/clopidogrel
- standard heparin
- IIb–IIIa antagonists
- low molecular weight heparin
- anti-vitamin K
- other

### 4 *Clinical outcome at 1 month*

All MACE should be carefully recorded.

### 5 *Follow-up at 6 months*

This includes a complete clinical follow-up as well as angiographic assessment by quantitative coronary angiography. Whenever possible, recurrent symptoms should be evaluated by some form of stress testing. Repeat angiography should be available in at least 90% of the initial cohort. The core laboratory should provide a clear description of the site of occlusion or restenosis, whenever applicable (intra-stent, presence of new lesions elsewhere).

### *Phase 4: clinical application (unlimited availability) and further clinical evaluation*

During the process of unrestricted clinical utilization, further trials involving several hundreds of patients are desirable. The results of a few completed randomized trials are currently available. Stents which work in a similar manner may be approached as a group, sharing the efficacy proven for the well established stents. However, given the different properties of the various stents, it is advisable that the lesion-specific indications of one vs the other stent (if any) continue to be investigated by appropriate studies.

## Long-term effects of coronary stenting

Whenever a new stent is being introduced for clinical application, a registry of the 1 year clinical outcome in the first 300–400 patients (including the cases involved in phase 3) should be organized by the company and the results made available. A registry is only meaningful if data are obtained *for all of the first 300–400 stents that are released*.

Admittedly, the life expectancy of patients with single-vessel disease, who still represent the majority of patients undergoing PTCA and stenting, is excellent and therefore, possible long-term effects of stenting could only become apparent in 10 to 20 years from now. Several publications on medium-term follow-up after stenting are available<sup>[55–60]</sup>, but further information after even longer periods is still awaited. In analogy to *post-marketing surveillance* with drugs, we would propose installing at the ESC (or national) level a vigilance committee to which physicians should report any long-term untoward effects, possibly related to prior stent implantation. Particular attention is needed for the following issues:

- Stent loss. Undeployed stents have been (and will be) lost in the systemic circulation and the possible consequences in the future, if any, remain unknown.
- Stent infection and coronary rupture<sup>[61,62]</sup>.
- In-stent restenosis. Although less likely to occur than after balloon angioplasty, clinical restenosis may still occur after stent implantation. The specific mechanisms that may be involved<sup>[63–69]</sup> and the most appropriate forms of treatment, including laser application,

radioactivity, or local delivery of anti-proliferative drugs require further prospective evaluation.

- Metal fatigue. This phenomenon is likely to occur with metal devices and was brought up on several occasions. However, the issue may not be important because of the fairly rapid inclusion of the stent in the vessel wall.

## Current indications for coronary stenting

As indicated earlier, stents are used in 30–60% of all coronary angioplasty procedures at most interventional centres. In this field, there is presently a significant but decreasing mismatch between clinical practices and trial-based evidence<sup>[70,71]</sup>. The positive results of the few available randomized trials have been enthusiastically extrapolated to almost every other patient and lesion subset. Hence, definitive evidence for the use of stents in several specific indications is still lacking. Current indications and the relevant evidence have been recently reviewed<sup>[72–74]</sup> and will be tentatively summarized below. A list of published or ongoing randomized trials on coronary stenting is given for indication in Table 2 and a more detailed review is available elsewhere<sup>[75]</sup>. The results of many of these studies will be available shortly and the indications will have to be adapted accordingly.

At present, there is solid evidence from randomized and observational studies to support the following indications:

- treatment of abrupt, and prevention of threatened, coronary occlusion after balloon angioplasty with various stents including the Gianturco–Roubin, the Wiktor, the Palmaz–Schatz, the Wallstent or the Microstent<sup>[10,21,23,56,76–94]</sup>
- primary reduction in restenosis, in non-restenotic focal lesions, in 3 mm vessels and particularly in the left anterior descending coronary artery<sup>[10,29–31,51,95–100]</sup>

There are ongoing randomized trials supporting the encouraging observational data which favour the use of stents for the treatment of:

- saphenous vein graft disease<sup>[14,27,60,101–113]</sup>
- suboptimal angiographic results after balloon angioplasty<sup>[77,94,114–117]</sup>

Randomized studies performed in a limited number of patients, as well as observational reports, seem to indicate a benefit of stenting for the treatment of:

- chronic total occlusions<sup>[118–122]</sup>
- restenotic lesions after prior balloon intervention<sup>[123–127]</sup>

Currently, the clinical use of intracoronary stents should be restricted to these indications.

As a corollary, further evidence is awaited before the routine use of stents can be recommended in clinical conditions such as acute myocardial infarction<sup>[128–131]</sup> or in other lesion subsets, such as ostial disease, long lesions, left main stenosis, small vessels, diffuse disease,

or bifurcation lesions<sup>[91,113,132–134]</sup>. In particular, it is not recommended to stent distal vessels at locations that may be suitable for graft implantation. We should avoid closing the opportunity of coronary artery bypass grafting to patients who are subjected to extensive stenting which covers the entire vessel. Lastly, the value of repeat stenting for in-stent restenosis has not been established.

## Future developments

New stenting strategies are under clinical evaluation and may reflect future evolutionary changes in the application of the technique.

The stent technique applied in the Benestent and Stress trials<sup>[29,30]</sup> involved (intended) single-stent implantation, following pre-dilatation of a discrete stenosis with an undersized balloon. Some of the new strategies involve the use of debulking techniques (rotational and directional coronary atherectomy or laser) prior to stenting<sup>[135]</sup> and endovascular reconstruction (implantation of long or multiple stents to cover all diseased segments of a coronary artery). Although the rationale (less obstructive plaque leads to improved stent expansion) seems appropriate, no evidence is available on the additional clinical benefit of mixing other revascularization techniques with stents. Multiple angioplasty devices will also add significantly to procedural costs. For routine practice, debulking should not be recommended and should be reserved for those situations where proper stent expansion is expected to be impossible (e.g. undilatable lesions, severe calcifications preventing high pressure balloon dilatation because of balloon rupture).

The concept of endovascular reconstruction is based on the following rationale<sup>[136]</sup>. Usually the stented coronary segment has smooth angiographical contours. After high pressure stent dilatations with slightly oversized balloons, the stent diameter exceeds the reference diameter, so that adjacent lesions that appeared non-significant, prior to stenting, may have a worse aspect after a stent has been implanted in the target segment. Since it is suspected that outflow obstruction of the stent is associated with a higher risk for subacute stent thrombosis, it is tempting to implant multiple stents in order to obtain a smooth angiographical result in the total coronary artery, even if there is no evidence of haemodynamically significant disease.

However, the effect of elective implantation of multiple stents or of long stents (e.g. 30 mm or longer), to reduce restenosis is not known from randomized studies. More thrombogenic material, overlap of stents, uncovered segments between stents may all have a negative effect on restenosis. This applies to implantation of multiple stents from different manufacturers, using different materials and concepts (e.g. balloon-expandable stents combined with self-expanding stents). In addition, considerable procedural costs may counteract the possible cost–benefit of restenosis prevention.

**Table 2** List of selected published and ongoing randomized trials on coronary stenting

Objective	Subset	Acronym		Stent	
A. Evaluation of revascularisation strategies	Single LAD disease	SIMA		stent vs CABG	JJIS
	Multivessel disease	ARTS SOS		stent vs CABG stent vs CABG	JJIS Crown several stents
B. Comparison with PTCA	Acute or threatened closure after PTCA	GRACE	[76]	stent vs balloon	Gianturco-Roubin
		TASC II STENT-BY	[77,78] [79]	stent vs balloon stent vs balloon	JJIS
	Native vessel, de novo stenosis	BENESTENT I	[29,31]	stent vs balloon	JJIS
		BENESTENT II	[51]	stent vs balloon	heparin coated JJIS
		STRESS	[30]	stent vs balloon	JJIS
		SLOMOS		stent vs balloon	long lesions
	Saphenous vein graft disease	START	[96]	stent vs balloon	JJIS
		WIDEST		stent vs balloon	Wiktor
		RAVES	[101]	stent vs balloon	JJIS
		SAVED		stent vs balloon	JJIS
	Chronic total occlusion	TECBEST		stent vs TEC	JJIS
		SPACTO		stent vs balloon	Wiktor
		SICCO	[119]	stent vs balloon	JJIS
	Acute myocardial infarction	STOP		stent vs balloon	AVE Microstent
ESCOBAR			stent vs balloon	JJIS	
PAMI STENTIM 2			stent vs balloon stent vs balloon	heparin coated JJIS Wiktor	
Restenosis after PTCA	REST	[123]	stent vs balloon	JJIS	
	WALLSTENT		stent vs balloon	Wallstent	
In-stent Restenosis	LARS		laser vs balloon		
				Gianturco-Roubin II vs JJIS	
C. Comparison between stents	Native vessel, de novo stenosis	GR II			Gianturco-Roubin II vs JJIS
		MULTI-LINK WIKTOR		ACS vs JJIS Wiktor vs Gianthurco- Roubin II	
D. Evaluation of adjunctive therapy	anticoagulation and antiplatelet regimen	GOY <i>et al.</i>	[93]	Wiktor vs JJIS	
		HALL <i>et al.</i>	[38]	aspirin with vs aspirin without ticlopidine	JJIS
		ISAR	[39]	aspirin with vs aspirin without ticlopidine	JJIS
		EPILOG		Reopro vs placebo	
		ERASER		Reopro vs placebo	
		FANTASTIC		warfarin vs ticlopidine	
		STARS		aspirin vs aspirin+coumadin vs aspirin+	
		TRAPIST		trapidil vs placebo	
		OPTICUS		ticlopidine	
		E. Prevention of in-stent restenosis	role of intravascular ultrasound	DEBATE II	
DEFER					
role of pressure and/or velocity wires	DISTRESS				
local heparin delivery	HIPS LIHPS				
systemic treatment	ERASER			Reopro vs placebo JJIS	

AVE=Arterial Vascular Engineering; JJIS=Johnson & Johnson Interventional Systems; LAD=left anterior descending coronary artery; PTCA=percutaneous transluminal coronary angioplasty.

Therefore, these and other new stenting strategies should be evaluated within the framework of well conducted prospective clinical trials.

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