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Drug-Eluting Stents in Preclinical Studies Recommended Evaluation From a Consensus Group

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The arrival of drug-eluting stents raises important questions about preclinical evaluation of devices and the optimal means of predicting clinical safety and efficacy. The Interventional, Regulatory, Commercial, and Scientific communities have all asked for assistance in defining criteria for device evaluation. This document is an integrated view of requirements for evaluating drug-eluting stents in preclinical models. The suggested requirements encompass study design, experimental performance, and histopathologic evaluations, emphasizing safety and efficacy at multiple points in time.

This is a consensus document assembled by clinical, academic, and industrial investigators engaged in preclinical interventional device evaluation. Suggested requirements might well serve as a standard but do not prescribe a single manner in which all devices should be evaluated. They instead motivate such an evaluation and describe how examinations might be performed. It is understood that methods will change and knowledge will evolve, in particular as corroboration is established with clinical data. The dynamic nature of this document allows for future modifications and additions.

Definition

A drug-eluting stent presents or releases single or multiple bioactive agents into the blood stream. The drug can deposit in and/or affect blood vessels, cells, plaque, or tissues either adjacent to the stent or at a distance. Systemic drug concentrations may be avoided or desirable. It is assumed that drugs undergoing preclinical evaluation will have sound theoretical

and practical reasons for biological success, and that the preclinical studies will help answer the magnitude and safety of effect when presented with or from the stent. It is likely that substantial empirical data already exists documenting the effects of these drugs on isolated cells in culture and even in vivo after systemic administration. Some drugs may already be in clinical use. Drug can be embedded and released from within ("matrix-type") or surrounded by and released through ("reservoir-type") polymer materials that coat ("strut-adherent") or span ("strut-spanning") the struts of the stents. In other formulations, the drug may be linked to the stent surface without the need for a coating by means of detachable bonds that release with time, can be removed by active mechanical or chemical processes, or are in a permanently immobilized form that presents drug to flowing blood. The stent platform may be a simple modification of clinically available devices or units specially designed for drug elution.

In Vitro and In Vivo Pharmacokinetics

Drug release should ideally be characterized both in vitro and in vivo. In vitro drug release should be examined at body temperature, under "infinite-sink" conditions, and with agitation to prevent boundary layer effects until completion of release or no significant change in release is further anticipated and in appropriate solvents as determined by the physico-chemical properties of the drug. Accordingly, it is advantageous to define these properties of the drugs, including, for example, diffusivity in free water and in the optimal solvent, solubility, oil:water partition coefficient, degree of

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protein binding, and molecular weight and charge. For example, the release of protein-binding drugs should be examined in protein-containing solutions. Elution features may differ across release platforms as well, and kinetics should be presented from the devices to be implanted. In contrast to release profiles from surface-bound drug or drug incorporated within nonerodible polymeric materials, release from erodible polymeric coatings can actually halt for some time and later resume, and these profiles should be described.

In vivo drug release can be characterized in a number of ways. Direct chemical determination of drug release or presence of radio- or fluorescent-labeled compounds in serum can be used to construct release curves. Drugs with first pass metabolism might be detected in urine. Alternatively, stents can be recovered at variable points in time after implantation and the amount of residual drug determined and used to extrapolate a release kinetic. When first-order release kinetics are observed, a release half-life ($t_{1/2}$) can be determined. Some investigators have suggested that a loose definition of half-life can be helpful for all release formulations when this parameter is defined as the time at which half of the drug has left the stent. The sensitivity of characterization can be maximized by frequent sampling. We recommend use of a minimum of 5 time points examining release from 3 separate stents.

Drug concentration in blood, in the coronary artery wall at the immediate implant site, and in myocardium directly beneath the stent should be measured at multiple time points. These times should cover the range of elution from immediately after implantation until the time when most of the drug is eluted. Drug concentration should also be measured in myocardium supplied by the stented artery segment in short-term, acute (hours–days) studies. Long-term drug concentrations in liver, kidney, and lung should also be measured at necropsy to verify whether any systemic effects are possible.

Several additional but optional measurements are desirable for in vivo pharmacokinetics estimation. These include (1) additional time points to more fully characterize drug release into arterial tissue and better definition of safety margin dose; (2) drug levels in arterial tissue proximal and distal to stent; and (3) drug levels in myocardial tissue proximal and distal to stent. Table 1 summarizes the pharmacokinetic recommendations.

Dose

The proposed clinical drug dose and release characteristics should be justified by preclinical data. Preclinical dose ranging is recommended, showing effects across ranges from subtherapeutic to toxic levels. Such a toxic high dose value could be, for example, within the range 3- to 10- times the anticipated clinical dose. This high dose will also be useful in estimating a safety margin, which is very desirable.

A dose representing a safety margin should be estimated and justified by the spectrum of biological responses in the multiple dosing study. A safety margin dose is one in which toxic effects are beginning to appear, or one in which higher doses show toxicity. This dose can later be used to justify safety for a clinically chosen dose.

Ideally, a multiple drug dose study should be performed in an animal model to establish safety margins, efficacy, and

TABLE 1. In Vitro and In Vivo Drug Release Characteristics

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- (1) In vitro half-life estimate, $t_{1/2}$, where half of all available drug has been released.
 - (2) In vivo peak tissue and blood concentrations, and a time-course graphic of drug remaining in the stent.
 - (3) In vivo $T_{1/2}$ estimate using a minimum of 5 time points each and 3 separate stents.
 - (4) A dose range showing subtherapeutic to toxic levels. A safety margin should be estimated and justified by data.
 - (5) Drug concentrations in blood, coronary artery, and myocardium beneath the stent over time points from immediately after implantation until near-complete drug elution. Drug concentration in myocardium supplied by the stented artery, liver, kidney, and lung, measured at necropsy.
 - (6) Optional: in vivo pharmacokinetics
 - a. Additional time points to more fully characterize drug release into artery tissue
 - b. Drug levels in arterial tissue proximal and distal to stent
 - c. Drug levels in myocardial tissue proximal and distal to stent
-

toxicity in choosing a dose for clinical trials. This may in fact be difficult to perform, as the amount of drug that can be possibly loaded on a stent may not be dramatically greater than that which is anticipated to minimally effective. When possible, then results obtained with the maximal possible loading of drug should be presented along with lower doses.

Stent and Drug Release in Cell Culture Studies

Biological effects seen in cell culture do not necessarily relate to in vivo activity. However, if the biological effects of the drug to be eluted are examined in cell culture, such experiments should utilize vascular endothelial and smooth muscle cells over a range of doses in a logarithmic scale.

Animal Models

The ideal animal model for drug-eluting stent evaluation is uncertain. It is almost certainly the case that drug deposition and pharmacological response will vary with arterial site and lesion morphology. Yet, it is unclear that any single animal species is any more predictive of human response and for specific indications. As such, we view animal models as providing mechanistic insight into fundamental biological processes. These models can therefore help prove critical hypotheses regarding putative mechanism of action of an intervention, but cannot be used to predict efficacy. There is no animal model of human vascular disease; there are only animal models of how devices will behave in well-characterized animal models. Proof of concept can be examined in animals — including evidence for toxicity based on expected understanding of the biology of the organism. True efficacy and safety can only be proven in man. It is therefore critical to construct human trials that resemble the animal preclinical trials and to make it clear what data and important conclusions can be justifiably extracted from animal models.

Experience suggests that the coronary arteries in domestic crossbred swine and iliac arteries of rabbits are suitable in that their size, access, and injury response are similar to human vessels, and therefore allow us to examine devices that might

TABLE 2. Histopathological Injury Score Quantitation

Numerical Score	Injury
0	Internal elastic lamina intact; endothelium typically denuded, media compressed but not lacerated
1	Internal elastic lamina lacerated; media typically compressed but not lacerated
2	Internal elastic lacerated; media visibly lacerated; external elastic lamina intact but compressed
3	External elastic lamina lacerated; typically large lacerations of media extending through the external elastic lamina; coil wires sometimes residing in adventitia

be used in clinical evaluation. Selection of devices with proper dimensions is essential, and stents should be appropriately sized to the artery in preclinical studies, because too much mechanical stent injury confounds safety and efficacy results. Safety and efficacy should be examined in a comparative study with several time points. A key safety concern is stent thrombosis. All animals experiencing death or other untoward clinical events should be examined and the stent status carefully documented, regardless of cause of death. Since standard stent practice in patients entails oral aspirin plus either clopidogrel or ticlopidine, these agents should be administered throughout the preclinical study.

Models, Pharmacokinetics, and Tissue Response

Porcine Coronary Artery Model

The porcine model of choice is the normocholesterolemic domestic crossbred, or mini-swine coronary artery. Stents should be appropriately sized for the artery (stent:artery ratio between 1.0 and 1.1) and implanted into coronary arteries with no prior injury. Double injury models are biologically interesting but offer enough variability in response that they cannot reproducibly test the questions at hand. Injury is best quantified by a traditional score (Table 2).

Peripheral porcine arteries do not develop neointima as vigorously as coronary arteries and are therefore less desirable for testing drug-eluting stents for coronary use. However, peripheral artery testing may be a good model for drug-eluting stents intended for peripheral implant.

Rabbit Iliac Artery Model

The rabbit iliac artery is a second, acceptable model choice. Rabbits may be normo- or hypercholesterolemic. As with the porcine model, stents should be appropriately sized (stent:artery ratio between 1.0 and 1.1) and implanted in arteries without prior injury.

This model is suboptimal for survivability since subacute cardiac events (eg, arrhythmias originating in downstream myocardium due to the drug itself) are not detectable in peripheral implants.

Drug-Eluting Stents and Controls

Only one stent should be implanted per artery except when issues of stent overlap or multiple stent dosing are considered. Stents may be placed in multiple different arteries in the same

animal including bare, carrier-only, and carrier plus drug-eluting stents. The stents should be "appropriately sized" by visual or quantitative coronary artery measurement with a stent:artery ratio $\leq 1:1$.

The choice of controls is slightly more complex. Polymeric materials for drug elution frequently affect the arterial repair process, generally in a toxic manner. When a drug is bound directly to a stent, the stent without drug can be a satisfactory control.

However, when a polymer or carrier of any sort is present, additional controls to evaluate the carrier alone, without the drug, must also be included. Coatings of polymer materials and stents not loaded with drug will react differently than coatings devoid of drug after complete release. This difference may reflect a difference in surface characteristic (eg, porosity, texture, etc), especially when matrix-type devices are used.

Overlapping Stents

Stent overlap frequently occurs during clinical implant, and overlapping drug-eluting stents present the possibility of a combined effect from drug released from the 2 stents. While avoiding overlap during initial evaluation, purposeful overlap should be performed in later studies. The distance of overlap should be roughly one third the length of a stent or 4 mm, and the number of overlapping stent implant pairs should be no less than 5. Histopathology processing should be done with sections taken from the reference segments, the single (non-overlapped) stented region, and the overlapping stented region.

Sampling Time Points and Sample Size

Stent efficacy should be assessed by an absent thrombosis and by neointimal reduction. Data should be obtained at an early time point (3 or 7 days) to help determine subacute thrombosis risk. Other time points used should be at 28 days to observe neointimal hyperplasia, and at least one late time point to examine long term effects. The late time point (3 or 6 months) depends on when "healing" and drug release are both complete. Note that the Food and Drug Administration typically recommends 6-month data for preclinical stent data. Three-month follow-up is generally acceptable for initiating Investigational Device Exemption clinical trials if no adverse findings are noted at this time. Six-month data should be pending at the time of Investigational Device Exemption submission, however. These later time points are especially important given the impact of peri-stent late remodeling as an additional cause of peri-stent effects that would impact the clinical outcome.

Long-term time points for animal studies (6 months or greater) are important, but results may be less rigorously interpreted until global understanding about the relationship between animals and patients at these longer implant times is obtained. These studies are pending currently. The choice of a long-term endpoint becomes far more complicated when dealing with drug-eluting stents. Whereas injury after balloon angioplasty or stent implantation may peak and the resolve over weeks to months, the presence of a drug might well change that dynamic. Ideally, tissue reactivity and whole

animal health should be examined for a multiple of the drug residence times within the primary target tissue. As a drug is typically cleared within 4 half-lives, we suggest waiting this period of time. Drug elution thus corresponds to 4 half-lives of the drug in the tissue after drug is no longer being perceptibly eluted from the release devices.

The number of stents for study should be determined from a power calculation for predetermined expected difference in key parameters. Sample size power calculations are not yet well defined, and so must be estimated. Typically, 7 to 10 drug-eluting stents per time point are satisfactory in most models.

Implant Procedure

Veterinary anesthesia should be established per accepted standard, in compliance with local Institutional Animal Care and Use Committee and Association for Assessment and Accreditation of Laboratory Care standards. Surgical technique for the procedure, including cutdown, catheters, wires, and other procedural equipment, may be at investigator discretion but in compliance with accepted standards.

Stent-Related Antiplatelet Medication

All animals may receive antiplatelet therapy (aspirin plus clopidogrel or ticlopidine) daily, beginning 1 day prior to the procedure and continuing for the duration of survival. Antiplatelet drug doses should be at investigator discretion.

Autopsy/Necropsy Evaluation

Necropsy is an important part of the stent evaluation process. All premature and unexpected deaths should be closely examined by necropsy, gross evaluation, and histopathologic examination. Special attention should be given to the stent(s) as possible causes. The term "procedural death" should be avoided or carefully explained and documented, recognizing that death after the first 24 hours both in pigs and in rabbits is rare, and may represent problems with the stent(s). Thrombus within the stent should undergo histopathologic examination, and it should be determined whether the thrombus occurred pre-mortem or post-mortem. In general, a variegated platelet-fibrin component, clot layering, clot adhesion to the vessel wall, and presence of polymorphonuclear leukocytes with cellular organization and maturation suggest pre-mortem stent thrombosis. Necropsy should be performed by a qualified individual to determine the cause of death for all animals dying after entry into the study, regardless of whether completing the allotted survival time or not. An opinion should be rendered as to cause of death when not due to euthanasia. The status of all stents in such early/unexpected deaths should be determined, recorded, and reported. The heart should be examined for any evidence of infarct or fibrosis, especially in the distribution and perivascular regions (respectively) of the stent implants.

Histopathology should be performed on all implanted stent-artery stents, including those dying any time after the procedure has begun. All implanted stents should be sectioned, regardless of how long they were implanted. The thoracic cavity (pigs) or abdominal cavity/retroperitoneum

(rabbits) should be examined for effusion, inflammation, infection, perforation, or other problem.

Tissue Processing and Fixation

Fixation is important for preserving artery size and shape. The precise method will be determined by the fixative required and analysis to be completed. Pressure perfusion should be performed at about 100 mm Hg and with rapid exsanguination. Immersion fixation should be performed in a volume sufficiently large to allow complete and rapid fixative percolation through the tissue and without alteration of the tissue shape. Following removal, the hearts or limbs containing the stent should be sectioned transaxially (short axis sections) at a minimum of 1-cm intervals. These sections should be examined grossly for evidence of myocardial or muscle infarction. All such infarctions should be included in the final report.

Histopathologic Stains, Histopathology, and Histomorphometry

Histopathology and histomorphometry are key to determining stent performance and effects, both positive or negative. Plastic or epoxy embedding is strongly recommended, as paraffin sectioning with strut removal disturbs tissue and cell relationships. Gross tissue effects can be visualized with Hematoxylin and Eosin (H&E), Elastin stains, and trichrome (preferably Masson's) stain alone. More specific cellular responses require specialty stains and immunohistochemical techniques. A representative number of sections should be taken to examine the entire stent, proximal and distal segments, and adjacent/affected tissues. A pathologist or other individual with extensive and specialized experience in microscopic examination of stented arteries must be the primary reviewer of tissue and stents, and should either perform or closely supervise other individuals performing measurements on the arterial sections. Such observations should be blinded to treatment group and should include proximal, mid, distal, and distal reference artery measurements (minimum 10 mm).

Clinical and Blood Parameter Evaluation

Animal well-being is an important observation following stent implant. Clinical features include normal physical signs and blood parameter measurements. The drug-eluting stent should have minimal effect on physical signs and clinical parameters in any animal implanted with a drug-eluting stent. The following should be documented in all animals: general health (daily record), body temperature at follow-up, and body weight over the course of the study. Myocardial infarction should be sought in the case of porcine coronary implant by performing electrocardiography at baseline compared with euthanasia.

Blood parameters should be measured to observe for allergy or liver or renal dysfunction. These measures should be done at baseline and at euthanasia, and include a complete blood count with differential, liver enzymes (alanine transaminase, aspartate transaminase), and creatinine. Particular drugs may have idiosyncratic effects on tissues and cells, and specific chemical parameters may need to be assayed in those instances.

Arteriography and Intravascular Ultrasound

Arteriography immediately prior to euthanasia can yield important information about the arterial lumen and patency within the stent. Arteriography should be performed immediately preceding euthanasia. Special attention should be paid to look for arteriographic peri-stent effects. Intravascular ultrasound (IVUS) may be performed in a minority of stents to examine for peri-stent effects and neointimal formation. Peri-stent effects are typically defined as including the 5 mm beyond the stent ends. IVUS is optional in the stented and reference segments and may be performed in a minority of cases, or more cases if desired by the investigator, as long as injury to the stented segment is avoided. IVUS can help answer questions concerning peri-stent effects when visualized by arteriography or subsequent pathological evaluation. However, routine IVUS in all animals may create the risk of damage to the stented artery and should be considered only after careful thought.

Stent Evaluation

Simple visual description of the histopathology is discouraged as the sole evaluation. A more rigorous, (semi)quantitative and defined scale for device evaluation should be presented as well.

Semiquantitative Histopathology

Injury and Inflammation

Inflammation by histopathologic evaluation can include an injury score (value 0 to 3) at each stent strut site, an inflammation description (absent, or cell types and location), and an inflammation score (value 0 to 3) for the overall vessel as well as for the adventitial, media, neointima, and at stent strut sites. When possible, cell density in tissue compartments should be recorded as number of cells per area.

Angiogenesis and Other Histopathology

Angiogenesis can also be recorded (value 0 to 3) and reported in the adventitia, media, and neointima. Other histopathologic features should be observed in the media, adventitial, and neointima, and assigned a value of 0 through 3 or a more quantitative parametric value such as number and size of vessels per unit area. These include fibrin or fibrinoid deposits, hemorrhage, and necrosis.

Observational Histopathologic Data

Endothelialization, Reendothelialization, and Vessel Healing

A healed vessel should show endothelialization or a healthy-looking layer of near-complete periluminal cells. Endothelialization should be recorded as absent, partial, or complete in all sections. Semiquantitative analysis can be performed and presented as the percentage of circumference covered by endothelium. The time of reendothelialization should be estimated. Scanning electron microscopy from 3 or more stents is recommended to assess endothelial recovery. Careful consensus consideration of a "healed" stent site also suggests that it demonstrates no evidence of fibrin, fibrinoid deposits, excessive inflammation, or hemorrhage.

Stent Strut Position and Adjacent Tissue

Other observational data should include stent strut apposition to the vessel wall (percent of wires in contact), and stent struts covered by tissue or endothelium (percent). A subjective description should also be rendered for adjacent tissue, including medial thinning, loss of cellularity, and hyalinization.

Myocardial Histopathology

Histopathology from the myocardium directly beneath, distal to, and supplied by the stent should be observed and recorded as normal or abnormal, and the same as or different from control stents. Specific attention should be directed at examination for myocardial infarcts.

Quantitative Histomorphometry

Histomorphometry of histopathologic sections is essential for stent evaluation. Measurement systems should be calibrated prior to each measurement session against a traceable standard. Measurements at all sections should include medial area, IEL area (area within the internal elastic lamina), EEL area (area within the external elastic lamina), lumen area, and stent area (area within the stent itself).

Neointimal measurement is important for efficacy assessment and should include thickness at each stent strut site and total neointimal area. The average neointimal thickness (average for all strut sites) should be calculated for each section. If there is separation of the stent struts from the IEL, each site should be measured and reported for distance of strut separation.

Derived Calculations From

Quantitative Histomorphometry

The following calculations from histopathologic information should be derived for each stent.

- Remodeling should be calculated for the mid-stent region as EEL area/EEL area proximal reference.
- Remodeling at the proximal and distal reference vessels should be calculated as reference IEL diameter/IEL diameter at midstent.
- Percent stenosis should be calculated 3 ways: (1) $100 \times (1 - \text{lumen area} / \text{IEL area})$; (2) $100 \times (1 - \text{lumen area} / \text{proximal reference area})$; and (3) $100 \times (1 - \text{lumen area} / \text{distal reference area})$.
- Peri-stent effects should be calculated as neointimal area proximal reference – neointimal area mid-stent.

Statistical Comparisons for Safety and Efficacy

Data analysis should include safety by specifically enumerating the parameters shown in Table 3. Efficacy should be quantitatively analyzed with a statistical comparison across groups for the parameters shown in Table 4. Values obtained along the length of an artery do not represent individual statistical events and should be averaged and used as 1 data point per segment.

Report Summary and Conclusions

The conclusion section should begin with a concise section stating motivation for the study design, for the doses chosen,

TABLE 3. Important Safety Features of Drug-Eluting Stents

Unexpected death and reasons
Clinical problems (death, fever, intolerance)
Stent thrombosis and/or infarctions
Myocardial infarction, acute and/or healed
Cellularity and description of drug-eluting vs control media
Medial area/presence or absence of medial thinning comparison
Inflammation at stent strut sites
Reaction to polymer/carrier
Endothelialization
Fibrin presence/degree
Angiographic and histopathologic stenosis

and for the time points used. These should be supported by pharmacokinetic data. Proposed safety margins should be determined and justified by the data. Toxicities should be described as evidenced by the data.

Study conclusions are crucial to understanding device safety and efficacy. These should be communicated clearly and concisely. Conclusions should not be simple data restatement, but instead should be an ordered, interpretive list reflecting stent safety, toxicity (including proposed toxicity margins), and efficacy. Each conclusion should reflect synthetic thought, well supported by study data. Appropriate use of representative graphics (charts, tables, etc) should be included to support and simplify the conclusions.

The report should first summarize and then synthesize conclusions. A general statement should be made based on study data indicating whether the drug-eluting devices performed better than control and polymer/carrier-only devices. If such a statement is not possible in broad terms due to mixed results, the efficacy statement should be explicitly enumerated for all of the above parameters separately. Ideally, the drug-eluting device should perform better than controls and polymer/carrier-only devices. At a minimum, the drug-eluting devices should not be worse than controls and polymer/carrier-only devices. The report should reference whether the stented vessels healed completely, partially, or not at all.

TABLE 4. Important Histopathological Efficacy Features of Drug-Eluting Stents

Lumen area
Percent stenosis
Neointimal area
Neointimal thickness
Medial thickness at stent strut sites
Medial thickness between stent struts
Remodeling
Injury
Inflammation
Radial gap width
Peri-stent segments
Overlap segments

Consensus Opinion: Satisfactory Findings and Outcomes

It is well recognized that scientific study results are frequently mixed, and that conclusions require interpretation. The study conclusions should reflect general success of a given device study, and should not be interpreted as rigid requirements. At this early stage of model development, it is not possible to make quantitative recommendations for efficacy. However, general guidelines may be proposed as follows.

Sudden Death

Experience with stented porcine coronary arteries suggests that sudden death may be more common in drug-eluting devices, principally due to platelet-rich coronary stent thrombosis. Such deaths typically occur in the first 24 hours after implant, but may occur later if healing is impaired. The early mortality rate for pigs should be less than about 15%. This is typically reduced when pigs receive 1 or 2 stents instead of 3, and may rise with use of mini-swine and animals less hearty than domestic crossbred swine. Sudden death later than 24 hours should be vigorously investigated for cause. Overall mortality, including early and late deaths, should be less than 25%. It should be recognized that the 25% level of animal death in a drug-eluting stent evaluation is quite high. A study with this much animal loss suggests a problem with either the devices or the implant methods and techniques. Any percentage of deaths higher than this number should be a warning of substantial problem somewhere in the study.

Inflammation and Fibrin Deposits

Polymer coatings by their nature typically induce inflammatory responses and fibrinoid deposits. This response may be acceptable if the reaction is minimal or mild, and does not accelerate, extend, or cause substantial vascular injury or stenosis. However, it is key that investigators demonstrate that such early inflammatory reactions meet the above safety criteria for later time points as well.

Neointima and Arterial Injury

Neointima should be thinner and/or of less cross-sectional area in drug-eluting devices for at least some of the measured time points. Histopathology showing excessive injury may occur, but should be present in less than 20% of sections. These should be quantified nevertheless, and an assessment should be made by the pathologist as to whether such injury resulted from the drug/polymer associated inflammation or mechanical injury. Conclusions of the study may be made without including such severely injured sections. The number of such excluded sections should be stated.

Overall Conclusions

This document is intended guide preclinical evaluation of drug-eluting stent technology. It represents a consensus opinion of active investigators in the field of interventional devices. It will be updated as needed and as experience gained with preclinical models permits better understanding of the important relationships between the models and the clinical results.

Additional Resources

- Bayes-Genis A, Camrud AR, Jorgenson M, et al. Pressure rinsing of coronary stents immediately before implantation reduces inflammation and neointimal hyperplasia. *J Am Coll Cardiol*. 2001;38:562–568.
- Carter AJ, Lee DP, Suzuki T, et al. Experimental evaluation of a short transitional edge protection balloon for intracoronary stent deployment. *Catheter Cardiovasc Interv*. 2000;51:112–119.
- Carter AJ, Lee DP, Yeung AC. “Metaling” with new stent designs. *Catheter Cardiovasc Interv*. 2001;53:426–428.
- Drachman DE, Edelman ER, Seifert P, et al. Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months. *J Am Coll Cardiol*. 2000;36:2325–2332.
- Edelman ER, Rogers C. Pathobiologic responses to stenting. *Am J Cardiol*. 1998;81:4E–6E.
- Edelman ER, Seifert P, Groothuis A, et al. Gold-coated NIR stents in porcine coronary arteries. *Circulation*. 2001;103:429–434.
- Ettenson DS, Edelman ER. Local drug delivery: an emerging approach in the treatment of restenosis. *Vasc Med*. 2000;5:97–102.
- Farb A, Sangiorgi G, Carter AJ, et al. Pathology of acute and chronic coronary stenting in humans. *Circulation*. 1999;99:44–52.
- Farb A, Heller PF, Shroff S, et al. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. *Circulation*. 2001;104:473–479.
- Garasic JM, Edelman ER, Squire JC, et al. Stent and artery geometry determine intimal thickening independent of arterial injury. *Circulation*. 2000;101:812–818.
- Holmes DR, Camrud AR, Jorgenson MA, et al. Polymeric stenting in the porcine coronary artery model: differential outcome of exogenous fibrin sleeves versus polyurethane-coated stents. *J Am Coll Cardiol*. 1994;24:525–531.
- Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. *Circulation*. 2001;104:600–605.
- Murphy JG, Schwartz RS, Edwards WD, et al. Percutaneous polymeric stents in porcine coronary arteries: initial experience with polyethylene terephthalate stents. *Circulation*. 1992;86:1596–1604.
- Nordrehaug JE, Priestley KA, Chronos NA, et al. Self expanding stents for the management of aorto-ostial stenoses in saphenous vein bypass grafts. *Br Heart J*. 1994;72:285–287.
- Schwartz RS, Huber KC, Murphy JG, et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. *J Am Coll Cardiol*. 1992;19:267–274.
- Schwartz RS. Characteristics of an ideal stent based upon restenosis pathology. *J Invasive Cardiol*. 1996;8:386–387.
- Schwartz RS. The vessel wall reaction in restenosis. *Semin Interv Cardiol*. 1997;2:83–88.
- Schwartz RS. Pathophysiology of restenosis: interaction of thrombosis, hyperplasia, and/or remodeling. *Am J Cardiol*. 1998;81:14E–17E.
- Serruys PW, Regar E, Carter AJ. Rapamycin eluting stent: the onset of a new era in interventional cardiology. *Heart*. 2002;87:305–307.
- Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. *Circulation*. 2001;104:1188–1193.
- Taylor AJ, Gorman PD, Kenwood B, et al. A comparison of four stent designs on arterial injury, cellular proliferation, neointima formation, and arterial dimensions in an experimental porcine model. *Catheter Cardiovasc Interv*. 2001;53:420–425.
- Thomas WJ, Laird JR, Bailey L, et al. Experimental results with the multi-link feminine stent in a porcine model. *J Invasive Cardiol*. 1997;9:453–460.
- Uren NG, Chronos NA. Intracoronary stents. *BMJ*. 1996;313:892–83.
- van Beusekom HM, Schwartz RS, van der Giessen WJ. Synthetic polymers. *Semin Interv Cardiol*. 1998;3:145–148.
- van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation*. 1996;94:1690–1697.
- van der Giessen WJ, Schwartz RS. Coated and active stents: an introduction. *Semin Interv Cardiol*. 1998;3:125–126.
- Verheye S, Salame MY, Robinson KA, et al. Short- and long-term histopathologic evaluation of stenting using a self-expanding nitinol stent in pig carotid and iliac arteries. *Catheter Cardiovasc Interv*. 1999;48:316–323.
- Virmani R, Farb A. Pathology of in-stent restenosis. *Curr Opin Lipidol*. 1999;10:499–506.