Fast-track article

Drug-eluting versus bare metal coronary stents: long-term human pathology. Findings from different coronary arteries in the same patient

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A 71-year-old woman underwent right coronary artery (RCA) bare metal stenting during an acute myocardial infarction. Seven months later the patient received a sirolimus-eluting stent as treatment for an 80% left anterior descending coronary artery (LAD) stenosis. She remained asymptomatic until she presented with unstable angina 16 months later. Angiography demonstrated subtotal occlusion of the left obtuse marginal branch. The LAD sirolimus-eluting stent showed 0% stenosis. The RCA stent showed 30% restenosis. The left obtuse marginal branch lesion was successfully stented, but the patient suffered a fatal stroke 24 hours after the coronary intervention. At autopsy the 16-month-old LAD sirolimus-eluting stent was widely patent with a minute thrombus near the ostium of a small side branch. The stent surface appeared free of any other irregularities. Scanning light microscopy showed mild neointimal thickening. Scanning electron microscopy showed > 80% endothelialization of the stent. The 24-month-old RCA bare metal stent showed mild to moderate neointimal growth with > 90% endothelialization.

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The past 2 years witnessed the extraordinary results of drug-eluting stents, placing this technique at the center of percutaneous therapy. A string of recent works suggests that drug-eluting stents might represent the first substantial documented therapy for the prevention of restenosis in *de novo* lesions[1,2], with a significant reduction in neointimal hyperplasia and target vessel reinterventions[3,4]. However, little is known on the long-term clinical effects of drug-eluting stents in humans. A recent clinical report on the first clinical experience with the sirolimus-eluting stent confirmed the long-term maintenance of the highly significant reduction in ischemic target vessel revascularization, without any excess of untoward events[5]. Nevertheless, animal data collected at the different time points of follow-up, supported the concept that the vascular responses to drug-eluting stents are in some way different from the pathology of bare metal stents[6,7]. In animal models, depending upon the drug potency and polymer biocompatibility, drug-eluting stents may suppress neointimal growth at the cost of a delayed healing process, with a lower rate of endothelial stent coverage, more persistent fibrin deposits and an increased inflammatory response[8]. Despite the tremendous expansion of the use of coronary stents, few data on the pathology of stents deployed in human coronary arteries have been published[9,10]. No pathological findings of drug-eluting stents implanted in humans have been reported yet. These results may provide insights into the biology of drug-eluting stents-vessel wall interaction and guide the long-term human clinical acceptance[11-13]. This present case is the first in which the long-term pathological findings of bare metal vs sirolimus-eluting stent (Cypher™, Cordis, a Johnson & Johnson Company, Warren, NJ, USA) in human coronary arteries are compared[14].

Case report

A 71-year-old woman underwent mid right coronary artery (RCA) primary stenting (Multi-Link™ stent 3.5 × 15 mm) during an acute inferior myocardial infarction. The infarct-related vessel was completely

occluded with TIMI 0 flow. The RCA lesion was first dilated and the stent was then placed. The angiographic outcome was excellent (Fig. 1, no residual stenosis and restored TIMI 3 flow). At the 7-month angiography follow-up the RCA was fully patent with a minimal in-stent restenosis (30% diameter stenosis, Fig. 2A). A new critical lesion (80% stenosis) was discovered in the proximal-mid left anterior descending coronary artery (LAD) (Fig. 2B-C). The patient was enrolled in the randomized study with the sirolimus-eluting Bx Velocity stent (RAVEL Trial) and randomized to receive a single 3.5 × 18 mm sirolimus-eluting stent. This lesion was first dilated with an undersized balloon. The sirolimus-eluting stent was then placed under intravascular ultrasound guidance, with no residual stenosis. The patient was asymptomatic at the time of her per protocol 6-month angiography follow-up; a 0% narrowing of the LAD sirolimus-eluting stent was measured at quantitative coronary angiography (Fig. 3). The intravascular ultrasound of the LAD confirmed the absence of any

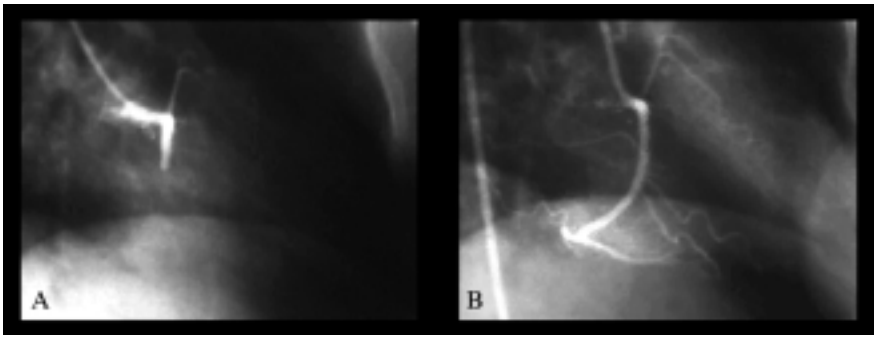

Figure 1. *Coronary angiography at the time of the acute inferior myocardial infarction.* A: *pre-procedure view, the right coronary artery is completely occluded in its mid segment, with TIMI 0 flow.* B: *end procedure after bare metal stent implantation, with no residual stenosis and a restored TIMI 3 flow.*

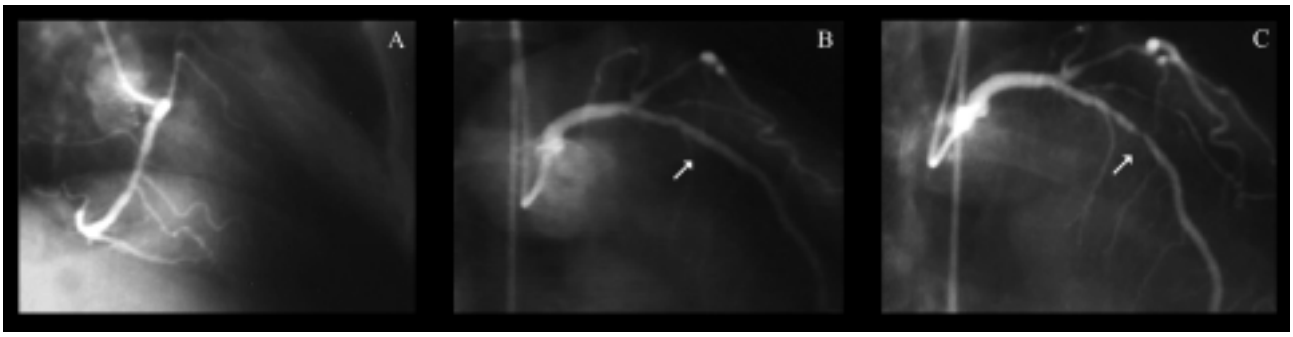

Figure 2. A: *the right coronary artery at the 7-month per protocol angiographic follow-up (right anterior oblique view). The stent was fully patent with a minimal in-stent restenosis.* B *and* C: *angiogram of the left coronary artery (antero-posterior cranial view) showing a critical lesion in the mid portion of the left anterior descending coronary artery (80% minimum lumen diameter stenosis) prior to angioplasty and sirolimus Bx Velocity stent placement.*

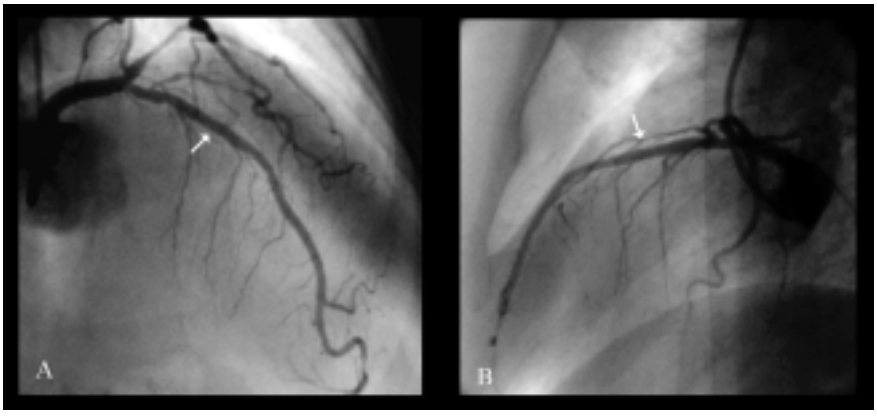

Figure 3. *Six-month per protocol angiographic follow-up (RAVEL Trial). Left anterior descending coronary artery sirolimus-eluting stent* (arrows)*: 0% narrowing at the stent level in two orthogonal projections (antero-posterior cranial and lateral views).*

neointimal proliferation across the entire length of the sirolimus-eluting stent (Fig. 4A).

The patient remained asymptomatic until 16 months after sirolimus-eluting stent placement (May 3, 2002) when she presented with episodes of chest pain at rest associated with mildly elevated serum troponin I levels (0.4 ng/ml). The patient received an upfront treatment with platelet glycoprotein IIb/IIIa inhibitors (eptifibatide double bolus + i.v. infusion). Urgent coronary angiography documented a subtotal occlusion on the left obtuse marginal branch with thrombus and TIMI 2 flow (Fig. 5A). A stainless steel (non-drug-eluting) Bx Velocity stent (3.0 × 18 mm) was placed in the left obtuse marginal branch with no final arterial stenosis and with a restored TIMI 3 flow (Fig. 5B). The LAD sirolimus-eluting stent (deployed 16 months previously) showed 0% restenosis (Fig. 6A-B). The RCA Multi-Link™ stent (deployed 24 months previously) showed 30% restenosis (Fig. 6C). The patient initially did well but she developed an ischemic stroke with a left hemisyndrome 24 hours following the coronary intervention. Due to an occlusion of the right mean cerebral artery, balloon angioplasty plus local fibrinolysis were immediately attempted. The local perfusion was reestablished in a large part of the vascular bed (Fig. 7A-C). One hour after cerebral angioplasty the patient's neurological picture rapidly deteriorated with loss of reflexes requiring intubation and assisted ventilation; serial computed tomographic scans performed during the next few days showed a massive cerebral

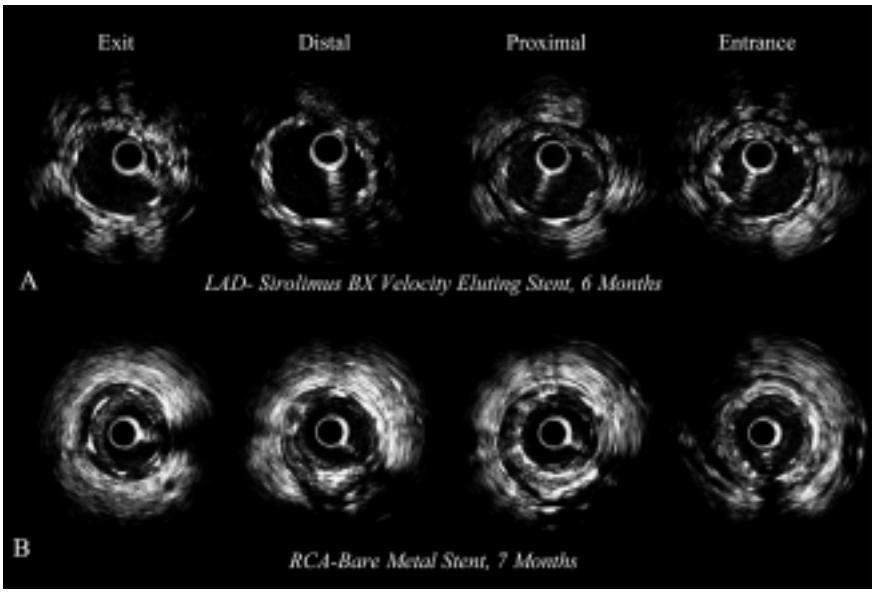

Figure 4. *Six-month intravascular ultrasound follow-up at different sections from the distal to the proximal reference segments. Four in-stent cross-sections (entrance, proximal, distal, exit) are shown.* A: *sirolimus-eluting stent, absence of neointimal growth across all the intravascular ultrasound sections.* B: *the 7-month intravascular ultrasound images of the Multi-Link™ bare metal stent implanted in the right coronary artery (RCA) are shown at the corresponding sections. Mild neointimal proliferation at the exit and across the distal and proximal sections. LAD = left anterior descending coronary artery.*

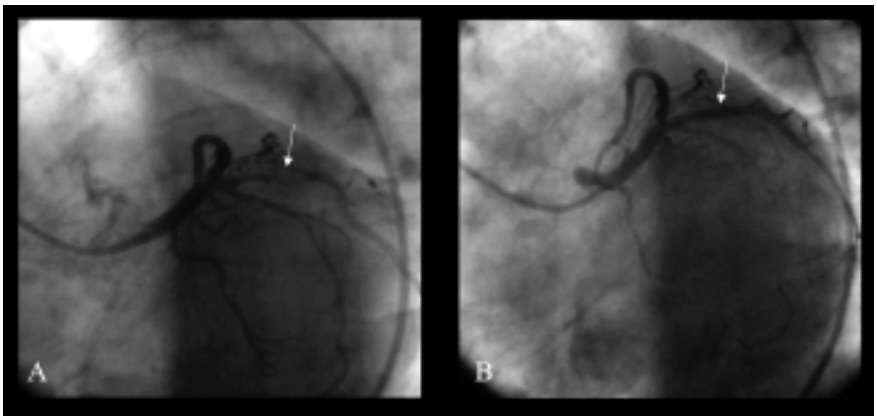

Figure 5. *Urgent coronary angiography performed on May 2002 due to unstable angina. Subtotal occlusion on the left obtuse marginal branch combined with a filling defect and TIMI 2 flow* (A). *Angiography (spider view) following predilation and placement of a non-drug-eluting Bx Velocity stent (3.0 × 18 mm). No residual stenosis and restored TIMI 3 flow grade in the left obtuse marginal branch* (B).

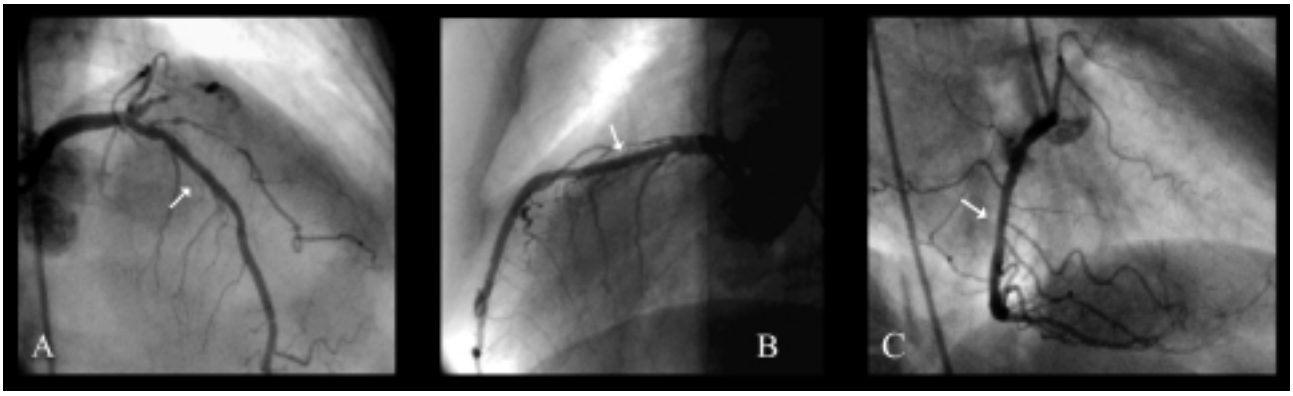

Figure 6. *No target vessel coronary angiography performed on the same day.* A *and* B: *the left anterior descending coronary artery (antero-posterior cranial and lateral views) 16 months following sirolimus-eluting stent placement* (arrows). *Long-term persistence of an optimal angiographic result with 0% narrowing at the stent level.* C: *the right coronary artery (right anterior oblique view) 24 months after the bare metal stent placement. Persistence of a good angiographic result with < 30% residual stenosis at the stent level.*

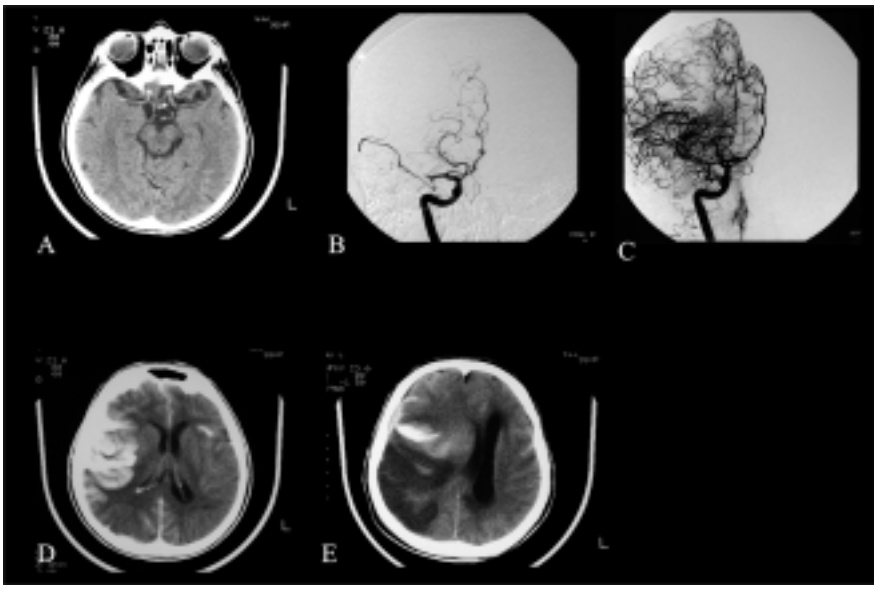

Figure 7. A: *computed tomographic scan performed 1 day after the percutaneous coronary intervention immediately after a stroke with a left hemisyndrome. There was no evidence of intracerebral bleeding.* B: *cerebral angiography performed 1 hour later, documenting thrombotic occlusion of the right mean cerebral artery.* C: *balloon angioplasty plus local fibrinolysis (urokinase 400 000 IU) was performed with reopening of a large part of the mean cerebral artery vascular bed.* D *and* E: *computed tomographic scans performed 1 and 3 days after. Evidence of massive cerebral damage and contralateral dislocation.*

damage with contralateral brain dislocation. The patient expired 10 days later due to a bulbar syndrome (Fig. 7D-E).

At autopsy (performed 16 hours after death) the 16-month-old LAD sirolimus-eluting stent was widely patent with a minute thrombus located toward the distal end of the stent, near the ostium of a small side branch (Fig. 8A). The stent surface appeared free of any other irregularities. Scanning electron microscopy of the one half of the LAD stent cut longitudinally showed > 80% endothelialization (Fig. 9A). There were focal, small areas of loosely formed endothelial cell junctions and occasional platelet aggregates close to the side branch ostium (Fig. 10B), associated with predominately pavement-shaped endothelial cells (Fig. 10A). The 24-month-old bare metal stent placed in the RCA showed mild to moderate neointimal growth without fibrin deposition. Scanning electron microscopy of the one half of the RCA stent cut longitudinally displayed > 90% endothelialization (Fig. 9B); the endothelial cells were longitudinally aligned with well developed cellular junctions (Fig. 10C-D).

Histology sections of the one half of the LAD sirolimus-eluting stent confirmed the presence of stent struts adherent to the vessel wall with a thin neointima consisting of smooth muscle cells and a collagen-rich matrix (Fig. 11A-B). Occasional fibrin deposits were identified near the stent struts, especially within the necrotic core, and were minimal within the neointima

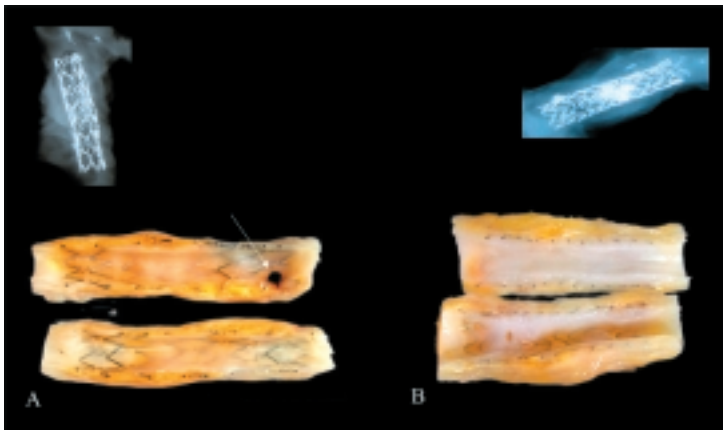

Figure 8. A: *post-mortem autoradiography and gross appearance of the 16-month-old left anterior descending coronary artery sirolimus Bx Velocity stent. The gross photograph of the longitudinally cut sirolimus-eluting stent shows a translucent neointima with the stent struts barely visible. A minute thrombus* (arrow) *was present at the distal end of the stent, near the ostium of a small side branch.* B: *post-mortem radiography and gross appearance of the 24-month-old right coronary artery Multi-Link™ stent. Gross photograph of the longitudinally cut Multi-Link™ stent showing an opaque neointimal appearance and no stent struts visible. Reprinted from Guagliumi et al.[14], with permission.*

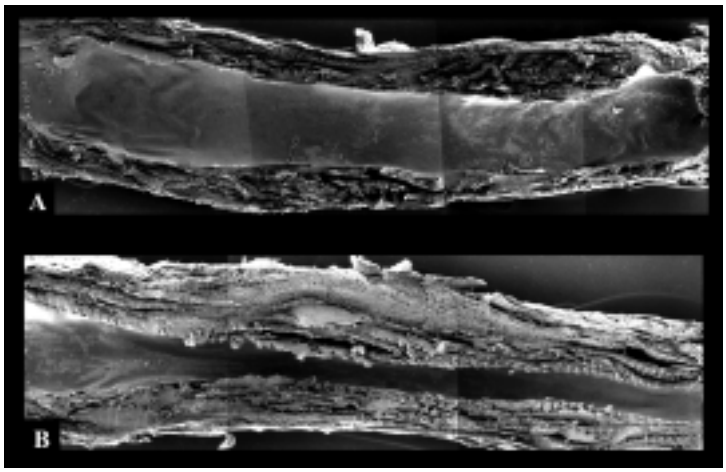

Figure 9. A: *low power scanning electron microscopy of one half of the longitudinally opened sirolimus-eluting stent. The surface appears covered by a thin endothelium. By visual estimation > 80% of the entire surface was reendothelialized. The proximal and distal 5 mm segments outside the sirolimus stent were fully endothelialized with a spindle shaped endothelium.* B: *scanning electron microscopy of the bare metal stent in the right coronary artery, 24 months following deployment; > 90% of the stent was covered by endothelium, with significant neointimal growth. Reprinted from Guagliumi et al.[14], with permission.*

(Fig. 11C). Inflammatory cells (mostly giant cells) were rarely observed. The polymer on the struts was identifiable but was not associated with inflammation (Fig. 12A-B).

The bare metal stent in the RCA showed prominent inflammation and neovascularization around the stent struts (Fig. 12C-D). The moderately thick neointima of the RCA stent consisted of smooth muscle cells in a collagen proteoglycan matrix; there were no fibrin deposits (Fig. 13).

The left circumflex stent was well placed with the stent struts penetrating the necrotic core; the stent surface was focally covered by fibrin and platelets without significant luminal reduction (Fig. 14).

In conclusion, 16 months after placement the thin neointimal healing of this sirolimus-eluting Bx Velocity stent was almost complete and consisted of smooth muscle cells in a proteoglycan and type III collagen matrix. Stent polymer covering was not associated with any inflammatory reaction. Only minimal inflammation and persistent fibrin deposition around occasional struts were observed despite lipid core penetration by the stent struts. Scanning electron microscopy showed almost complete endothelialization (> 80% covered by a paved shape endothelial lining) with focal loosely formed endothelial junctions and a small lumen thrombus with rare platelet microaggregates toward the distal end of the stent.

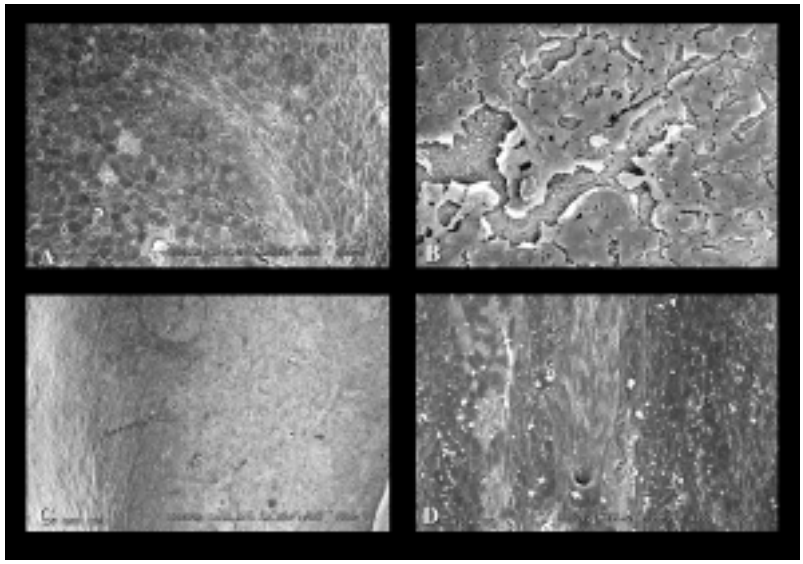

Figure 10. *High power scanning electron micrographs of one half of the longitudinally opened stents. Sirolimus Bx Velocity stent, 16 months after stent placement. The endothelial cells were pavement-shaped, with focal loose cellular junctions between adjoining cells* (A) *and occasional small aggregates of platelets close to the distal end of the stent* (arrow in B). C *and* D: *scanning electron micrograph of the bare metal stent in the mid right coronary artery, 24 months following deployment; the cells were spindle-shaped, longitudinally oriented, with well formed cellular junctions, with occasional platelet aggregates.*

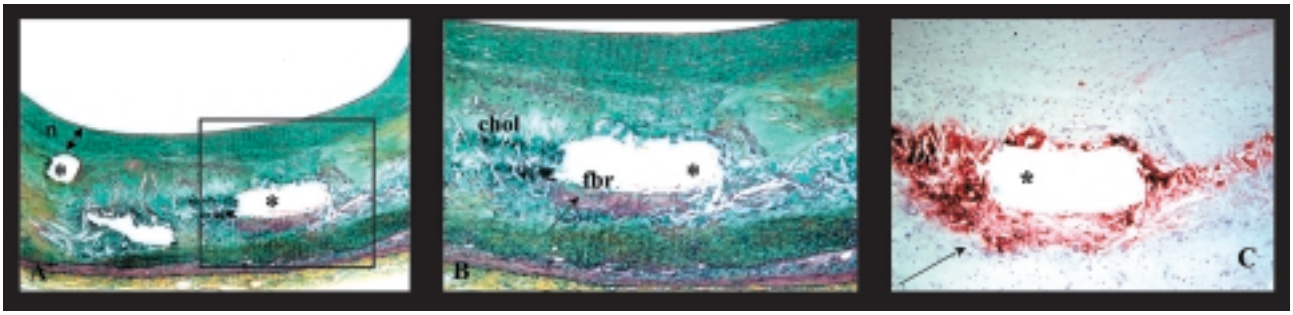

Figure 11. A: *low power microscopy of the 16-month-old sirolimus Bx Velocity stent. Note the strut (*) embedded in the lipid core. The neointima (n) is minimal and even overlies the strut in the lipid core.* B: *high power image of the strut in the lipid core. Note the cholesterol clefts (chol) and fibrin (fbr) deposition* (arrow) *around the strut.* C: *high power microscopy, persistent fibrin deposition* (arrow) *associated with the strut* (*).

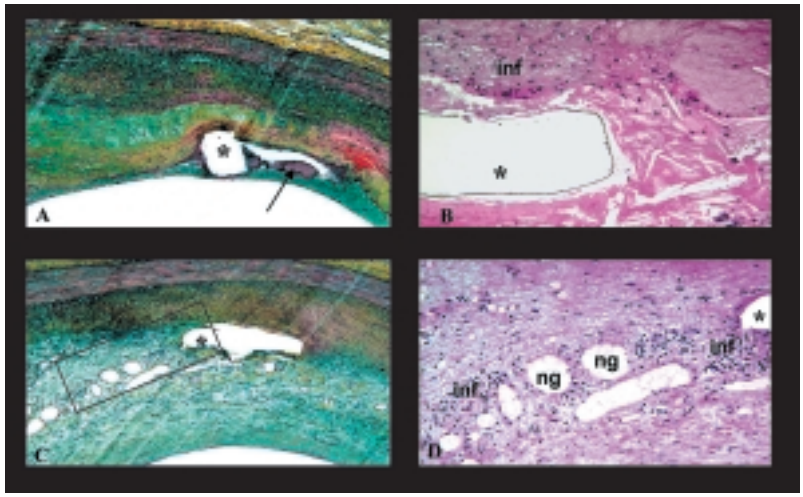

Figure 12. A *and* B: *light photomicrographs of the sirolimus Bx Velocity stent. Stent strut* (*) *with minimal associated inflammation* (arrow in A). *Strut polymer covering without an associated inflammatory reaction.* C *and* D: *light microscopy of the 24-month-old bare metal stent in the right coronary artery. Photomicrographs show moderate chronic inflammation (inf), highlighted area in* C, *with significant neoangiogenesis (ng) associated with the stent struts* (*).

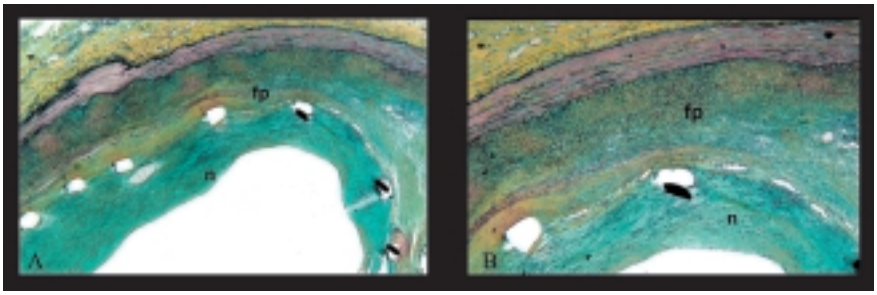

Figure 13. A *and* B: *low and high power light microscopy of the 24-month-old bare metal stent implanted in the right coronary artery. A moderately thick neointima (n) overlies the strut and is associated with fibrous plaque (fp).*

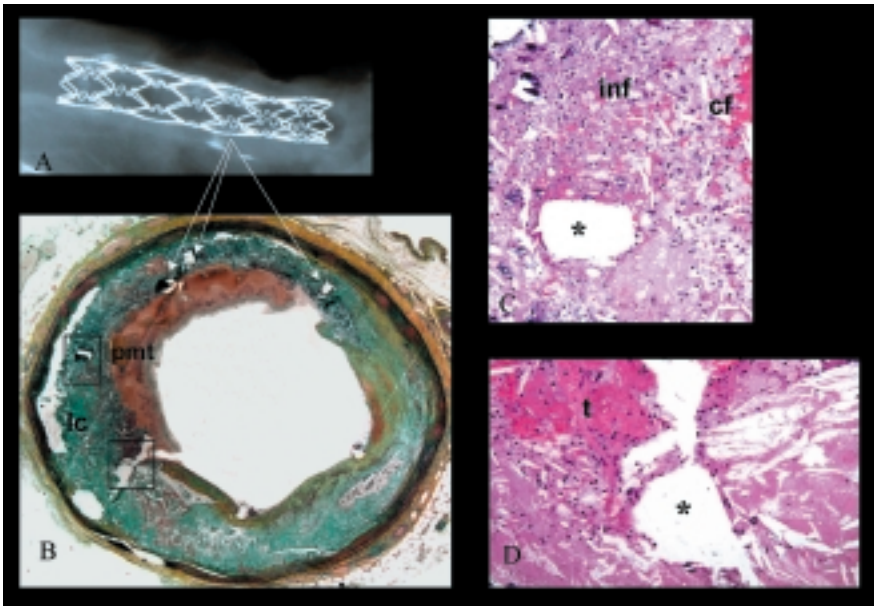

Figure 14. A: *post-mortem radiograph of the Bx Velocity bare metal stent implanted in the left obtuse marginal branch.* B: *light microscopy demonstrates a widely patent lumen with multifocal fibrous cap disruption and multiple stent struts* (arrows) *embedded in the lipid core (lc). A large post-mortem thrombus (pmt) is present, with small fibrin rich thrombi associated with the stent struts.* C: *high power microscopy of the strut* (*) *in the lipid core* (upper box in B). *Note the cholesterol clefts (cf) and the chronic inflammatory cells (inf).* D: *the strut* (*) *in the core* (lower box in B) *with an overlying fibrin-rich thrombus (t).*

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