

Drug-Eluting Stents in Angina

Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med. 2008;13:277-287

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One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease...

N. Mercado and others. *J Thorac Cardiovasc Surg.* 2005

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Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis

C. Stettler and others. *Lancet.* 2007

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D. E. Cutlip and others. *Circulation.* 2007

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Cyphering the complexity of coronary artery disease using the Syntax score to predict clinical outcome...

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P. Garg and others. *J Am Coll Cardiol.* 2008

Selection of seminal papers by
William Wijns, MD, PhD, FESC
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Highlights of the years by **Ian Mudway, MD**
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One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials

N. Mercado, W. Wijns, P. W. Serruys, U. Sigwart, M. D. Flather, R. H. Stables, W. W. O'Neill, A. Rodriguez, P. A. Lemos, W. A. Hueb, et al

J Thorac Cardiovasc Surg. 2005;130:512-519

With the advent of a safe and progressively more effective percutaneous coronary intervention (PCI) for coronary artery disease (CAD) as apposed to traditional coronary artery bypass grafting (CABG), the choice as to the best revascularization strategy for multivessel disease patients remains today still very challenging. Many previous meta-analyses have pooled together available randomized controlled studies comparing percutaneous versus surgical revascularization in such patient populations. However, they are limited by inclusion of patients treated with balloon angioplasty, with use of bare-metal stents restricted to bailout situations. The results of trials that antedated the stent era are not reflective of the current practice of coronary revascularization because coronary stents are nowadays implanted in approximately 90% or more of all procedures and adjunctive pharmacologic therapy with glycoprotein IIb/IIIa inhibitors is frequently used.

This systematic overview based on individual patient data from recent clinical trials comparing angioplasty with multiple stenting against CABG surgery thus provides the clinician caring for patients with multivessel disease with meaningful treatment effect estimates regarding the advantages and drawbacks of each treatment strategy. The authors created an individual patient database composed of 4 trials (Arterial Revascularization Therapies Study [ARTS], Stent or Surgery [SOS] trial, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease-2 [ERACI-2], and Medicine, Angioplasty, or Surgery Study-2 [MASS-2]) that compared percutaneous coronary intervention with multiple bare-metal stenting (N=1518) versus CABG (N=1533). One year after the initial procedure, PCI with multiple stenting and coronary artery bypass graft surgery provided a similar degree of protection against death, myocardial infarction, or stroke for patients with multisystem disease. Repeat revascularization procedures remain high after PCI, but the difference with CABG surgery has narrowed in the era of bare-metal stenting. In particular, the observed gap with CABG surgery has narrowed

from approximately 30% reported in the pre-stent era to approximately 14% in the present report.

While this analysis is largely consistent with the data reported by single studies comparing PCI versus CABG and the results showed in previous meta-analyses, there are some outstanding considerations, which should be kept in mind when interpreting the data. The main limitation of this meta-analysis is the relatively short follow-up period limited to 1 year. Long-term (5-year) follow-up of this cohort of patients is planned and will likely be reported soon. It is also likely that the patients included may represent a selected population of low-to-moderate risk patients with multisystem disease, thus limiting the generalizability of the results to more complex subsets of patients. Finally, the use of drug-eluting stents may significantly impact on the performance of PCI versus CABG in this patient population. With unrestricted use of drug-eluting stents, the difference in reintervention disfavoring the PCI approach may further be reduced without affecting the overall composite of death, myocardial infarction, or stroke. This is what has been shown in the ARTS II study in which 606 multivessel disease patients undergoing treatment with sirolimus-eluting stents were compared with historical results obtained in the CABG arm of ARTS I. The SYNTAX study (SYnergy between PCI with TAXus and cardiac surgery) compared in a prospective randomized manner multiple DES implantation versus CABG in patients with 3-vessel disease and/or left main stem-stenosis. The 1-year primary end point results of this study were presented at the European Society of Cardiology annual congress in September 2008.

2005

King Fahd of Saudi Arabia dies at the age of 83 and Crown Prince Abdullah accedes to the throne;

Cuban singer Ibrahim Ferrer, vocalist of the Buena Vista Social Club, dies aged 78 years; and Phil Mickelson wins the 2005 PGA Championship



Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis

C. Stettler, S. Wandel, S. Allemann, A. Kastrati, M. C. Morice, A. Schömig, M. E. Pfisterer, G. W. Stone, M. B. Leon, J. S. de Lezo, et al

Lancet. 2007;370:937-948

The long-term safety of the first two polymer-based drug-eluting stents (DES) approved by the US Food and Drug Administration (FDA)—a sirolimus-eluting stent and a paclitaxel-eluting stent—is a matter of intense and ongoing debate, with some studies reporting increased rates of death, myocardial infarction, or late stent thrombosis compared with bare-metal stents (BMS). These studies were, however, hampered by the small number of patients, limited durations of follow-up, or observational study designs.

Network meta-analyses allow a unified, coherent analysis of all randomized controlled trials that have compared either of the two DES with BMS or the two DES head-to-head, while fully respecting randomization. The authors set up a collaborative group of investigators who provided trial data based on standardized definitions of outcomes and performed a network meta-analysis. Thirty-eight trials (18 023 patients) were included with a follow-up of up to 4 years. Trialists and manufacturers were also contacted to provide additional data on clinical outcomes for 29 trials. This network meta-analysis showed that DES and BMS were associated with similar rates of overall and cardiac mortality, and that use of sirolimus-eluting stents was associated with a reduction in the risk of myocardial infarction compared with use of BMS and paclitaxel-eluting stents. About 100 patients must receive sirolimus-eluting stents, rather than BMS or paclitaxel-eluting stents, to prevent 1 myocardial infarction over 4 years. Although there was little evidence of an overall increase in definite stent thrombosis associated with DES, paclitaxel-eluting stents were found to be associated with an increased incidence of late stent thrombosis compared with BMS and sirolimus-eluting stents. However, it should be emphasized that wide confidence intervals precluded definite conclusions about a potential increase in late stent thrombosis with sirolimus-eluting stents compared with BMS.

A secondary analysis showed a marked reduction in target-lesion revascularization with both DES, which was more pronounced for sirolimus-eluting stents than for paclitaxel-eluting stents. About 6 patients must receive a sirolimus-

eluting stent rather than a BMS to prevent 1 target lesion revascularization over 4 years; 35 would need to receive a sirolimus-eluting rather than a paclitaxel-eluting stent to prevent 1 such event. Lastly, there was little evidence of an increased risk of mortality associated with either DES in diabetic patients, but again wide confidence intervals precluded definite conclusions.

This network meta-analysis integrated evidence from direct and indirect comparisons while fully preserving randomization. The considerably higher number of patients and events in this study, compared with previous analyses resulted in a relevant gain in statistical precision, particularly for the hazard ratio of death, myocardial infarction, and stent thrombosis. Network meta-analysis makes similar assumptions to standard meta-analysis of direct within-trial comparisons, but requires that these assumptions hold over the entire set of trials in the network, including the assumption that relative treatment effects comparing two interventions in different trials are from the same common distribution. The smaller the heterogeneity between trials, the more likely relative treatment effects originate from the same distribution. Additional assumptions are that the model fits the data and that the network of trials is consistent. Importantly, all assumptions were satisfied for all outcomes, except for stent thrombosis and target-lesion revascularization. Critics have argued that not all bare-metal stents included in the trials perform equally well, which makes pooling of outcomes problematic.

2007

The Roman Catholic Archbishop of Bulawayo
calls for mass protests to force Zimbabwe's
President Robert Mugabe from office;
The Scout Movement celebrates its centennial;
and Angola joins OPEC

Clinical end points in coronary stent trials: a case for standardized definitions

D. E. Cutlip, S. Windecker, R. Mehran, A. Boam, D. J. Cohen, G. A. van Es, P. G. Steg, M. A. Morel, L. Mauri, P. Vranckx, et al; Academic Research Consortium

Circulation. 2007;115:2344-2351

For every clinical cardiologist and cardiovascular researcher, this consensus article calling for standardized outcome definitions in coronary stent trials should be compulsory reading. Variability in end point definitions creates a formidable barrier to the understanding of results across clinical trials or the pooling of results for the detection of rare safety signals. With the recognition that consistency across well-considered end point definitions is critical to this process, 4 academic research organizations involved in the design and management of current drug-eluting stent (DES) clinical trials combined efforts in an informal collaboration termed the Academic Research Consortium (ARC) to orchestrate a set of consensus definitions for DES study end points.

While this consensus document focuses on the definitions and standardization of all clinical cardiac and cardiovascular end points that may be applicable to coronary stent trials, including death, myocardial infarction, reintervention in the target vessel and cerebrovascular accidents, the added value of this report is that it is the first attempt to propose a universal definition for stent thrombosis.

The ARC consensus is that both levels of evidence and timing of events can be stratified to define varying degrees of certainty and to imply different pathophysiological mechanisms, respectively. The triple level of certainty classification recommended is definite, probable, and possible stent thrombosis.

Definite stent thrombosis classification requires angiographic or autopsy confirmation, is highly specific, and is patterned on the definition developed when these events were first detected during early brachytherapy clinical trials. Although it maximizes specificity, the definite classification may not be sufficiently sensitive for the capture of a relatively rare safety event. The categories of probable and possible stent thrombosis add such sensitivity, but the utility of these categories will vary depending on the quality of data available to the adjudication committee. This is particularly true for the least specific thrombosis category, possible, which could be assigned to all late deaths unless

sufficient detail is provided for adjudication. It is important to avoid the dilution of a potential real difference in events with the use of an overly sensitive definition that may include cases unlikely to represent thrombosis. The ARC recommends the combination of adjudicated definite and probable stent thrombosis to best characterize this aspect of DES safety; however, the reporting of definite only and overall rates is also encouraged.

Since this report, the endorsement of this classification system for defining stent thrombosis has been widespread and consistent by both investigator- or sponsor-driven clinical trials, thereby resulting in a significant improvement in our understanding on the incidence, predictors, and clinical implications of stent thrombosis. This very sensitive definition of stent thrombosis, however, has clear limitations, which should also be acknowledged, including the fact that it labels as potential stent thrombosis almost any vessel or stent failure or even any unexplained fatal or nonfatal cardiac event in the presence of limited available information. This may be particularly problematic in studies recruiting patients who have an intrinsic risk of fatal or nonfatal recurrences, such as those with ongoing myocardial infarction. In such settings, the category of possible stent thrombosis remains questionable today. Similarly, it is likely that the specificity of probable and possible stent thrombosis categories decreases over time, which may impact on studies with long and clinical outcomes. A similar effort pertaining to appropriate end points for use in postmarketing surveillance registries would be welcome.

2007

Eleven World Wrestling Entertainers are suspended for suspected steroid abuse; World Rally champion Colin McRae and his son are killed in a helicopter crash in Scotland; and melting sea ice in the Arctic Ocean opens up the Northwest Passage between Europe, Asia and North America



Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern

E. Camenzind, P. G. Steg, W. Wijns

Circulation. 2007;115:1440-1455

At the European Society of Cardiology (ESC)/ World Congress of Cardiology (WCC) in Barcelona in 2006, some of us were caught off guard by a plenary session combining three critical presentations by Edoardo Camenzind, Salim Yusuf, and Alain Nordmann, who raised serious concerns about the long-term safety profile of drug-eluting stents (DES). This session was dubbed the "ESC firestorm" and is very well known to all updated interventional cardiologists. The criticisms and concerns regarding the safety profile of the first-generation DES, namely, sirolimus-eluting and paclitaxel-eluting stents, are summarized in this comprehensive revision of the literature.

The first section of this paper is devoted to the pathophysiology of stent thrombosis, which is attributed to the so-called Rudolf Virchow's triad: (i) abnormal vessel wall lining (eg, incomplete endothelialization); (ii) abnormal blood-flow pattern (eg, slow flow); and (iii) altered blood constituents (eg, increased blood thrombogenicity). Any of these items alone or in combination favors intravascular thrombus formation. The connection between the anti-restenosis effect of first-generation DES and late stent thrombosis resides in the fact that antiproliferative agents such as sirolimus or paclitaxel inhibit intimal hyperplasia growth and endothelial cell proliferation, which ultimately prevents stent strut coverage. First-generation DES inhibit or may even abolish vessel wall healing, leaving the struts in direct contact with flowing blood and blood elements. Complete or partial lack of reendothelialization of stent struts and vessel wall generates a long-lasting, if not permanent, unhealed vessel wall surface, favoring platelet adhesion and aggregation, which may eventually cause thrombus formation. Moreover, the chronic inflammatory process is possibly linked to the nonerodable polymer or the eluted drug itself may trigger positive vessel remodeling (ie, an increase in vessel luminal diameter over time). Widening of the coronary lumen over time may reduce both intra-stent flow velocity and wall shear stress. Segmental slow flow may be caused by a local intravascular abnormality (eg, aneurysm or bifurcational stenting) or a global coronary perfusion abnormality (eg, diastolic coronary perfusion

determined by variables such as tachycardia, increased tele-diastolic pressure, microangiopathy, distal embolization), and thereby give rise to prolonged interaction between vessel wall and blood constituents. According to this hypothesis, patients with delayed or poor stent healing after intervention who are at increased risk for late stent thrombosis are those who show no in-stent intima hyperplasia at follow-up and/or positive vessel remodeling.

Thus, particularly those DES that are associated with lower late loss (ie, higher intima hyperplasia inhibition) may predispose to higher likelihood of stent thrombosis. This hypothesis is challenged by several reports showing that the probability of late and especially very late stent thrombosis is slightly higher with paclitaxel-eluting stents than sirolimus-eluting stents, yet negative late loss at angiographic follow-up is more frequently detected in the latter than in the former. While this hypothesis remains intriguing, it needs to be proven by scientific trial before being endorsed by the cardiological community.

The second part of the article focuses on the rate of overall death or Q-wave myocardial infarction in first-generation DES vs BMS studies. The discussion emphasizes the need for a standardized definition of major cardiovascular safety end points and calls for a more transparent and systematic report of long-term outcomes in these studies. This report triggered intense scrutiny of all related issues and "carved some peepholes in the DES industry firewalls" (Cook et al, *EurIntervention* 2008;3:535-537).

2007

News Corporation's CEO Rupert Murdoch announces a \$5 billion takeover of Dow Jones & Co, the publisher of the Wall Street Journal;
Street Sense wins the 133rd Kentucky Derby;
and Floyd Mayweather Jr defeats Oscar De La Hoya in the highest grossing boxing match in history

Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents? Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents

P. W. Serruys, J. Daemen

Circulation. 2007;115:1433-1439

This position paper, intended as a point-by-point rebuttal to the paper by Camenzind et al, is a thorough reanalysis of the issue of early and late stent thrombosis (ST), starting from the introduction of the bare-metal stent (BMS), through the advent of brachytherapy, and finally focusing on drug-eluting stent (DES) data.

The authors questioned the scientific value of the classic triad of Virchow (altered blood constituents, flow pattern, and endothelial lining) as an explanation for ST after DES implantation. Discontinuation of oral antiplatelet treatment (aspirin and/or clopidogrel) is associated with proinflammatory and prothrombotic effects in patients with coronary artery disease, and this proved to be a risk factor for coronary events regardless of whether a DES was implanted or not. The optimal duration of dual antiplatelet treatment after DES remains currently unknown and clopidogrel discontinuation may be a risk factor for ST only when interrupted in the early phase after stenting (first 6 months), whereas there are currently no sound data in favor of more prolonged dual antiplatelet treatment. In a limited number of DES patients, postmortem findings show dramatic and compelling evidence of impaired reendothelialization with uncovered stent struts in stented arteries. However, eminent pathologists are the first to admit that postmortem studies have failed to evidence a common denominator and that the number of patients treated with DES in whom “uncovered stent struts” do not lead to ST is unknown, but undoubtedly very large.

Although late acquired malapposition has been occasionally observed with BMS, it is more frequent with DES, and the question remains of whether it has an unfavorable prognosis with respect to late ST. Intravascular ultrasound studies in randomized trials (RAVEL, SIRIUS, and E-SIRIUS), are available in 325 patients and the incidence of incomplete stent apposition at 6 months was 25% in the sirolimus-eluting stent (SES) group vs 8.3% in the BMS group. The authors found no prognostic impact of incomplete stent apposition on death (2.2% with incomplete stent apposition vs 5.2% without) and major adverse cardiac events

(8.9% with incomplete stent apposition vs 12.6% without) in patients treated with SES, at least in the short term. Late ST was observed in only 1 of 45 patients with incomplete stent apposition at a 6- to 8-month follow-up.

Finally, the authors critically reanalyzed the data presented at ESC 2006 by Camenzind et al during the “firestorm,” pointing out two potential methodological limitations:

- The meta-analysis was derived from data published at different time points of follow-up. Of note, more complete data only became available following the alarm.
- Camenzind took two hard clinical end points, total death and Q-wave myocardial infarction (MI), and disregarded non-Q-wave MI, which was indeed substantially lower in the Cypher group. By including all MI in the analysis, no increase in the composite of death or MI would be reached in the SES as compared with the BMS arm.

The authors concluded that late ST occurs both with DES and BMS. However, the chronology and circumstances of occurrence seem quite different. With DES, late ST occurs later than with BMS and seems to appear as primary thrombosis, whereas with BMS it may be related to repeat interventions of the target lesion. It is not known to which extent crossover to DES for treatment of BMS restenosis contributes to these events. Dedicated research is warranted to further elucidate the role of endothelial dysfunction, malapposition, and prolonged antiplatelet therapy. Currently, second-generation DES are attempting to resolve the problems posed so far by first-generation DES.

2007

A tsunami occurs on the northern coast of Japan following a 6.9 magnitude earthquake;
French presidential candidate Nicolas Sarkozy resigns as Interior Minister to concentrate on his campaign; and the European Union celebrates the 50th anniversary of its foundation



Drug-eluting stent update 2007: Part I. A survey of current and future generation drug-eluting stents: meaningful advances or more of the same? Part II: Unsettled issues

J. Daemen, P. W. Serruys

Circulation. 2007;116:316-328 (Part I, issue No. 3)

Circulation. 2007;116:961-968 (Part II, issue No. 8)

Part I is a comprehensive review of the past, present, and foreseeable future of drug-eluting stents (DES), whose numbers keep growing in an exponential manner. They are all loaded with drugs that interfere with inflammation and neointimal proliferation pathways. The process of restenosis is a sequence of complex events that has been only partly elucidated over the last 2 decades. Locally acting DES provide an opportunity to interfere with the various mechanisms responsible for each step in the restenotic cascade, and a wide variety of different agents are currently available.

The limus family is discussed first, which includes sirolimus-, everolimus-, zotarolimus-, pimecrolimus-, biolimus-, and tacrolimus-eluting stents, followed by paclitaxel-eluting stents. The new coating and new platform chapters are worth reading for those of us who want to understand who is doing what in a complex system such as DES technology nowadays. The pro-healing section is entirely devoted to a dream that has still to come true: we do have to inhibit intimal hyperplasia, but at the same time we also have to promote complete healing shortly after the implantation of the stent to obtain both lower late loss and an ideal safety profile. The so-called "endothelial progenitor cell (EPC) capture stent" which is coated with anti-CD34 monoclonal antibodies is here extensively described. EPCs are, however, not only identified by the expression of CD34 antigen, so the concept of a stent, which, by binding to CD34+ circulating cells, is able to promote stent healing is, to some extent, conceptually misleading and still waiting for proof-of-concept evidence. Indeed, today there is no clear-cut evidence suggesting that this complex type of device actually promotes quicker and more complete healing than the bare-metal stent, while the results in terms of late loss are partially disappointing. The last paragraph emphasizes the importance of elution kinetics as one of the most important variables for obtaining enduring late loss inhibition over time and for avoiding the so called late "catch-up phenomenon."

Part II is entirely devoted to unsettled issues in the DES era. After a brief summary focusing on the value of DES implantation as an effective means to reduce late loss and subsequent target-lesion revascularization as compared with BMS, the article focuses on the pitfalls of DES.

First, DES have been shown to hamper the natural vascular healing process. Second, stent underexpansion (minimum stent area <5.0 mm²), a factor linked to restenosis, is significantly more frequent after DES implantation. Whereas stent underexpansion is observed in 20% of all restenotic BMS lesions, an incidence of up to nearly 70% is reported in restenotic DES lesions. This may simply reflect a less aggressive policy of stent overexpansion after DES implantation as compared with BMS, due to excessive confidence in the anticipated superior antirestenotic properties of DES. Third, DES implantation seems to be associated with significant impairment in endothelial function, which in turn has been repeatedly linked to a higher rate of late adverse events. Fourth, recent reports have shown a significantly lower rate of neointimal coverage with DES (13.3% to 66%) than with BMS (90% to 100%), and subclinical thrombi tended to be more common with DES ($P<0.09$). These observations are pertinent to the concerns with late stent thrombosis, which is here extensively discussed both in the context of on- and off-label use of DES as compared with BMS.

2007

New species of scallop and octopi are discovered off the coast of Nova Scotia; Bollywood actor Sanjay Dutt is jailed for six years on charges of obtaining weapons from gangsters in a case associated with the 1993 Mumbai bombings; and New Zealand launches its first commercially available biofuel, consisting of 90% petrol and 10% bioethanol derived from cows' milk

Cyphering the complexity of coronary artery disease using the Syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention

M. Valgimigli, P. W. Serruys, K. Tsuchida, S. Vaina, M. A. Morel, M. J. van den Brand, A. Colombo, M. C. Morice, K. Dawkins, B. de Bruyne, et al; ARTS II

Am J Cardiol. 2007;99:1072-1081

Since the earliest reports of coronary angiography, the extent of coronary artery narrowing has been considered a primary determinant of survival in patients with coronary artery disease. The simple division into one-, two-, and three-vessel disease has provided a convenient scheme for classifying patients and it has been extensively employed across the literature. This straightforward scoring system, however, is known to underestimate the prognostic importance of anatomy, especially in patients with complex and diffuse coronary artery disease. The Syntax score (SXscore) was developed in the context of the SYNTAX trial (SYnergy between PCI with TAXus and cardiac surgery) as a comprehensive angiographic tool. The score merges and tailors several previously validated scoring systems to the current era of intervention, and aims to assist in patient selection and risk-stratification for individuals with extensive coronary artery disease undergoing revascularization.

This report compares the predictive value of the Syntax score and of the modified American Heart Association (AHA) lesion classification system. The Syntax score was applied to 1292 lesions in 306 patients undergoing treatment for three-vessel disease in the Arterial Revascularization Therapies Study part II (ARTS II) to examine its role in predicting short- and long-term incidence of major adverse events.

The Syntax score predicted the rate of major adverse cardiac and cerebrovascular events (MACCE), with patients in the highest score tertile showing a significantly higher event rate at both 30 days and 1 year. After adjustment for all potential confounders, including clinical presentation and lesion characteristics, the Syntax score remained an independent predictor of MACCE at 1 year's follow-up, with an almost threefold increase in the risk of events in patients in the highest compared to two lowest score tertiles. A better goodness of fit was obtained when modeling the risk provided by the Syntax score than that by the modified AHA lesion classification. This implies a closer relationship between observed and predicted event rates when the Syntax score is employed. In keeping with previous analysis,

the area under the curve for the Syntax score was greater than the AHA score for MACCE at 30 days. Similarly, using a time-dependent analysis, based on the c-index computation, the prognostic accuracy provided by the Syntax score was confirmed to be significantly higher.

The ultimate goal for the Syntax score will be to discriminate outcome in surgically versus percutaneously treated patients, in view of selecting the best revascularization strategy for the individual patient. The prognostic implications of the Syntax score for patients with three-vessel and/or left main coronary artery disease undergoing either percutaneous or surgical coronary revascularization will be further evaluated in the ongoing trial. As soon as this dataset is available, each single item of the Syntax score will be "weighed" according to discrepancy between observed and predicted event rate in order to further optimize calibration and the interaction between the global score and its single components as well as with the mode of revascularization applied (ie, percutaneous versus surgical). While still clearly in its early phase, the Syntax score will likely be complemented in the future by surgical risk scores, such as the Euroscore or derived scores, to better determine the optimal revascularization strategy in patients with complex coronary artery disease.

2007

India's Essar Group buys Canadian steelmaker Algoma for \$1.63 billion; Author Ray Bradbury and jazz saxophonist John Coltrane receive special citations at the 2007 Pulitzer Prize awards; and shootings at the Virginia Polytechnic Institute and State University leave 33 dead and 29 others wounded



Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study

J. Daemen, P. Wenaweser, K. Tsuchida, L. Abrecht, S. Vaina, C. Morger, N. Kukreja, P. Jüni, G. Sianos, G. Hellige, et al

Lancet. 2007;369:667-678

This cornerstone paper stems from the institutional databases of two tertiary referral centers in Europe, namely, Bern and Rotterdam. Between April 2002, and December 2005, 8146 patients underwent percutaneous coronary intervention in these two hospitals with either sirolimus-eluting stents (SES; n=3823) or paclitaxel-eluting stents (PES; n=4323). Angiographically documented stent thrombosis occurred in 152 patients (incidence density 1.3 per 100 person-years; cumulative incidence at 3 years 2.9%). Early stent thrombosis was noted in 91 (60%) patients, and late stent thrombosis in 61 (40%) patients. Definite late stent thrombosis occurred steadily at a constant rate of 0.6% per year up to 3 years after stent implantation. The incidence of early stent thrombosis was similar for SES (1.1%) and PES (1.3%), but late stent thrombosis was more frequent with PES (1.8%) than with SES (1.4%; $P=0.031$). At the time of stent thrombosis, dual antiplatelet therapy was being taken by 87% (early) and 23% (late) of patients ($P<0.0001$). Independent predictors of overall stent thrombosis were acute coronary syndrome at presentation (hazard ratio, 2.28; 95% CI, 1.29-4.03) and diabetes (2.03, 1.07-3.83). The median time to occurrence of early stent thrombosis was 4 days (inter-quartile range [IQR], 1-6). Of the 61 late stent thrombosis cases, 36 (59%) patients developed stent thrombosis 1 year or later after stent implantation (median, 451 days; IQR, 211-665). The cumulative incidence of stent thrombosis over time showed an initial steep rise with 50% of cases occurring within 9 days, followed by an almost linear increase in the remaining events up to 3 years. Notably, the absence of clopidogrel treatment did not seem to be associated with an increased risk of total and late stent thrombosis. The main value of this combined, yet retrospective analysis, consists in providing strong and worrisome evidence that the rate of late stent thrombosis does not decrease over time at least up to 3 years after drug-eluting stent (DES) implantation.

The hot issue we still need to clarify today is whether the rate of very late stent thrombosis will somehow flatten at longer-term follow-up or will this constant 0.6% rate per year be observed even beyond 3 to 4 years after DES implanta-

tion. Only longer-term follow-up studies will tell. Concomitantly, the major limitation of this analysis lies on the lack of a control group treated with bare-metal stent (BMS). Indeed, based on all randomized controlled studies conducted so far, it seems that the overall incidence of stent thrombosis does not differ in BMS- versus DES-treated patients. Thus, it is likely that BMS implantation is associated with a higher risk of stent thrombosis from 5 to 12 months after treatment, whereas DES use increases the likelihood of late stent thrombosis beyond 1 year. Based on these considerations, if the cumulative rate of late stent thrombosis will keep accruing over time after DES, at very long-term follow-up, the overall stent thrombosis rate may end up being significantly higher than after BMS implantation. This may translate into a net increase in the composite of death and myocardial infarction in the DES- compared with BMS-treated patients at very long-term follow-up. Careful long-term clinical surveillance of all DES and BMS patients so far recruited in randomized controlled studies will be pivotal for this purpose. Finally, in a consistent manner, PES was associated with slightly more late stent thrombosis than SES.

This has one major implication: even first-generation DES cannot be considered as one class of devices, and to some extent each single DES differs from the other, both in terms of efficacy and safety.

2007

The Virginia General Assembly votes unanimously in favor of a motion expressing “profound regret” for Virginia’s role in the promotion of slavery; Mario Chanes de Armas, one of the leaders in the Cuban revolution, dies, aged 80 years; and “The Departed” wins four Academy Awards including Best Picture and Best Director for Martin Scorsese at the 79th Academy Awards

Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization

A. V. Finn, M. Joner, G. Nakazawa, F. Kolodgie, J. Newell, M. C. John, H.K. Gold, R. Virmani

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Polymer-based sirolimus- (Cypher) and paclitaxel-eluting (Taxus) drug-eluting stents (DES) have become a treatment of choice for patients with symptomatic coronary artery disease undergoing percutaneous coronary revascularization. Although these stents have reduced rates of restenosis and late lumen loss compared with bare-metal stents, late thrombosis, a life-threatening complication of this technology, has emerged as a major concern. Although clinical predictors such as withdrawal of antiplatelet therapy are known to play a role in determining the probability of late stent thrombosis, the specific morphometric and histological parameters that significantly correlate with late thrombosis remained largely unknown.

This study reported by Finn et al was based on analysis of autopsy material and using a database of all patients dying >30 days after Cypher or Taxus DES implantation. It sought to determine the most powerful pathological risk factors for late thrombosis and identify the high-risk features of DES that might be clinically assessable. The main finding was that nonuniform healing with DES (as indicated by the number of uncovered struts per cross section) greatly increases the thrombotic risk.

Previous pathological studies have shown an association between lack of neointimal strut coverage and thrombus formation. Although the mechanisms by which the current-generation DES induce nonuniform incomplete healing are not fully understood, lesion characteristics, drug properties, dose, and distribution, and polymer biocompatibility together likely play an important role.

The underlying plaque morphology may affect the rate of healing when stent struts penetrate deeply into a necrotic core and are not in contact with cellular areas. Eccentric plaques may prevent uniform strut deployment, thereby increasing local toxicity resulting from higher concentrations of drug and polymer. Indeed, sections with evidence of thrombosis showed significantly lower inter-strut distances, which correlated with less neointimal growth. Local concentrations of drug are ultimately highly spacing-de-

pendent, and the variance in distance between struts amplifies differences in concentrations, leading to biological effects. Heterogeneity in loaded dose of drug varies from strut to strut, and greater retention of lipophilic drugs in different regions of plaque affects arterial drug concentration and results in nonuniform healing. The relationship between local drug concentrations and cellular repair is underscored by data from overlapping versus nonoverlapping Cypher and Taxus stents in the rabbit iliac model.

This study was seminal in establishing a predictor of late stent thrombosis. The authors speculated that there might be a continuum of risk increasing with the ratio of uncovered to total struts per section. Using a univariate logistic regression model of occurrence of thrombus in a stent section versus ratio of uncovered to total struts per section, they showed that in a stent with 30% uncovered struts, the odds ratio for thrombus is 9.0 (95% confidence interval [CI], 3.5 to 22.0) compared with a stent with complete coverage. Based on this postulation, many groups around the world are now evaluating, in vivo, using optimal coherence tomography, the predictive value of uncovered struts to identify upfront patients at high risk for very late stent thrombosis. This may have relevant implications for long-term management, including intensification and/or tailoring of antiplatelet treatment to protect patients from potential catastrophic consequences. Prospective studies to validate these pathologic findings in vivo are warranted.

2007

UK Prime Minister Tony Blair announces he will step down from office on the 27th of June 2007; Malietoa Tanumafili II, Samoa's Head of State, dies, aged 94; and Canada defeats Finland 4-2 to win the 2007 World Hockey Championship in Moscow



Balancing the risks of restenosis and stent thrombosis in bare-metal versus drug-eluting stents. Results of a decision analytic model

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Decisions regarding percutaneous coronary intervention (PCI) for obstructive coronary disease have become increasingly challenging for patients and physicians since the observation of delayed stent thrombosis with drug-eluting stents (DES). The main risk attributable to bare-metal stenting (BMS) was restenosis, requiring repeat revascularization—a risk that largely ended within 1 year after stenting. Beyond this period, events attributable to the stent were rare. In particular, in-stent thrombotic complications occurred in <1% of patients, almost exclusively within the first month after BMS implantation. By limiting neointimal hyperplasia within the stent, the current generation of DES has reduced the relative risk of restenosis by 50% to 70%. However, there is concern that DES might be associated with increased risks of delayed stent thrombosis.

In this study, the authors sought to quantify the degree to which current uncertainty in the rate of very late thrombotic complications after DES implantation would affect the choice of one stent type versus the other. Because both the absolute risk and duration of risk of stent thrombosis after DES implantation are uncertain, the authors used the Markov model of decision analysis to define what threshold of incremental risk of thrombosis with DES would outweigh the benefits of reduced restenosis in clinical practice. They found, on the basis of the best data currently available, that the DES strategy was preferred for a prototypical PCI patient under the assumption of no difference in the rates of (very) late stent thrombosis. Although the benefit was small in absolute terms (0.014 QALYs, or quality-adjusted life years gained), this gain is plausible given the time-limited nature of the restenosis process and the absence of long-term mortality benefit associated with restenosis avoidance in most studies. This finding was confirmed to be robust, on the basis of probabilistic sensitivity analysis, which takes into account a range of plausible probabilities rather than relying on fixed estimates alone. Nonetheless, the authors also found their results to be highly sensitive to the absolute risk and duration of risk for late stent thrombosis, leading to uncertainty about optimal decision over a range of risk that is plausible on the basis of current data. In par-

ticular, for a prototypical patient, the authors found that even a small excess risk of very late stent thrombosis (>0.14%/year over 4 years) would be sufficient to negate any advantage of DES over BMS in terms of mean quality-adjusted life expectancy. Furthermore, if the at-risk period extended beyond 4 years, the incremental annual risk that could be tolerated was even smaller.

Whether the true risk of very late thrombosis with existing DES exceeds this risk is uncertain at present. Most likely, the risk depends on stent type and patient/lesion subsets. Restenosis risks can be predicted with reasonable precision in overall populations and according to well-understood patient and lesion-based factors, because restenosis was a frequent occurrence over the past decade of practice. In contrast, stent thrombosis risks have only recently been studied with similar rigor. Although pooled analyses of randomized trials of the two approved DES platforms to 4 years of follow-up have not shown significant differences in risk of thrombosis between DES and BMS, the confidence intervals of these estimates are wide, suggesting that up to a 1.4% absolute risk difference at 4 years cannot be excluded.

In other terms, on the basis of a decision analytic model incorporating the best data currently available, the authors found that even a small (<1%) incremental risk in thrombosis with DES was sufficient to outweigh the benefit of restenosis prevention and favors BMS use for the overall PCI population. This analysis argues against the systematic use of first-generation DES in all cases; instead DES should be preferentially used in patient/lesion subsets with a high likelihood of restenosis when treated with BMS.

2008

Silvio Berlusconi is sworn in as the Italian Prime Minister for his fourth term in office; a pro-Europe coalition wins the Serbian parliamentary election; and a magnitude 7.9 earthquake hits China's Sichuan province, with at least 22 000 casualties