Drug-eluting coronary stents long-term hazard – Fact or fiction?

Nicolae FLORESCU, MD

"Carol Davila" University of Medicine and Pharmacy,
Cardiology Department, University Hospital of Bucharest, Romania

Interventional cardiology continues to evolve rapidly for a relatively mature field. Advances in percutaneous therapy (PCI) have occurred since the introduction of balloon angioplasty which involved a substantial periprocedural risk, due to occurrence of acute or subacute coronary closure in 5 to 10% of cases; restenosis was common, occurring in 40% to 50% of treated vessels within the first post-PCI year. In the mid 1990s the emergence of bare metal stents (BMSs) and new highly effective antiplatelet therapies reduced the acute complications of coronary intervention. The improvement of long-term outcomes based on BMS was not as dramatic as the improvement in procedure-related safety, although the risk of restenosis dropped in half, from 40% to 50% to 20% to 25%. Almost two million coronary interventions were performed worldwide in 2003, with a long-term risk of clinical events because of restenosis as high as 300,000 major cardiac clinical events per year and 150,000 clinical events secondary to recurrent restenosis. The restenosis has been therefore a vexing and costly problem for interventional cardiologist, even more important for some patient subsets, particularly diabetics (1).

From this standpoint, the availability of drug-eluting coronary stents (DESs) has represented a major advance in percutaneous therapy of coronary artery disease. Overall risk of restenosis of treated coronary arteries has decreased to a 5% to 10% in-stent restenosis rate; this significant improvement was associated with a marked reduction in the need for target vessel revascularization (TVR) and therefore considered as associated with improved clinical outcomes (1). DES coated with both sirolimus (SES) and paclitaxel (PES) have been studied, and no substantial difference in outcomes yet is apparent based on the drug. The first generation DESs – CYPHER® (Cordis, Johnson and Johnson) and TAXUS® (Boston Scientific) – have quickly become by far the most common form of stent in use, with more than 3 million patients treated worldwide, and more then 4,5 million DES implanted worldwide at the beginning of 2005. The penetration of DES use has been shown to be as high as 90% in the United States and 50% all over Europe.

However, more recent studies have highlighted that there may be a price to pay for this reduction in restenosis: a higher incidence of stent thrombosis, particularly late stent thrombosis. This is precipitated by delayed healing, is clearly temporally linked with discontinuation of antiplatelet therapy and may warrant more prolonged therapy than with bare metal stents. Stent thrombosis is a catastrophic event, associated with a high mortality (up to 45% case fatality) (2). Recently, two studies have highlighted

that this phenomenon is not trivial: the BASKET LATE data, presented by Dr Pfisterer at the ACC scientific sessions in March 2006 are follow-up data from a pragmatic randomized clinical trial performed in Basel in which PCI patients were routinely randomized to treatment with a drug eluting or a bare metal stent. In that analysis, after discontinuation of dual antiplatelet therapy at 6 months, the clinical event rate in the subsequent months was worryingly high: 4,9% of the patients with drug eluting stent experienced cardiac death or MI in the subsequent year, compared to 1,3% in those patients with bare metal stents (p = 0,01). The recent data from the PREMIER registry have highlighted that a large number of patients discontinue thienopyridines prematurely (up to 1 in 7 patients in the first 30 days) and this is associated with increased mortality in the next 11 months (7,5 vs. 0.7% p<0,0001) (3).

Finally, it is still largely unknown whether late stent thrombosis is a time limited phenomenon. It has been hypothesized that late stent thromboses may continue to accrue over time in the long term with drug eluting stents. If this might be true, this would soon become a major clinical problem with already a base of millions of drug eluting stents placed in patients.

A meta-analysis of first generation DESs – both first generation DES – comparing extent of both mortality and Q-wave Myocardial Infarction in comparison to bare metal stents, was presented by E. Camenzind (Geneva, Switzerland) at World Congress of Cardiology, held in Barcelona. Of the SES program the following trials were included: RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS and for the PES program: TAXUS II, IV, V and VI accounting for a total of n = 878 SES vs. n = 870 BMS and n = 1685 PES vs. n = 1675 BMS. The clinically oriented analysis has been focused on death, Q-wave MI and death and Q-wave MI combined thought to reflect the incidence of stent thrombosis. The incidence – up to the latest available follow-up – of total mortality and Q-wave MI combined were 38% (SES) and 16% (PES) higher in 1st generation-DES as compared to control BMS (p-value: SES vs. BMS: 0,03 ; PES vs. BMS. 0,68). In this meta-analysis, death and Q-wave myocardial infarction (MI) have had a higher incidence in 1st generation drug eluting stents as compared to the bare metal control stents. Thus, author has concluded that the indiscriminate use of 1st generation-DES should be avoided

and the use of bare metal stent may still be maintained waiting for safer 2nd generation-DES. Other separate, independent meta-analysis conducted by A. Nordmann has also suggested DES might increase death, Q-wave myocardial infarction and cancer deaths, bringing the long-term safety of DES firmly into the spotlight (4). As a direct result of this concern, the use of DES has declined worldwide since disclosing these data. Is this concern real or overbid?

A special "hot" session on DES safety topics was scheduled during Transcatheter Cardiovascular Therapeutics (TCT) Congress, held in October 2006 in Washington DC. Nine clinical trial databases (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS and TAXUS I, II, IV, V and VI) were obtained from industry by the Cardiovascular Research Foundation (CRF) with permission for unrestricted physician-directed analyses (G. Stone, M. Leon et al.), by an academic statistician (M. Fahy) (5-14). Both safety and efficacy data were reviewed: death (all, cardiac and non-cardiac), MI (all, Q-wave and non-Q-wave), death and MI, cardiac death and MI, death and Q-wave MI, stent thrombosis, target lesion revascularization (TLR) and target vessel revascularization (TVR). No composite end-points were analyzed, such as MACE or target vessel failure. That was strongly different from other previous analyses on DES safety issues; for e.g. In BASKET-Late Trial, the primary end-point was composite of cardiac death or nonfatal MI, and other end-points were so-called "thrombosis-related events". The latest follow-up time interval available was 4 (four) years. There were no significant differences between DES and BMS on total mortality, cardiac mortality, MI or stent thrombosis (Figure 1). Only significant difference between DES and BMS was noted in stent thrombosis occurring after 1 year; according to these date, there is no difference in overall stent thrombosis between 1st generation DES and BMS, but in timing of occurrence. DES might be more prone to thrombosis (very) late, yet this excess of late thrombosis is not translating in an excess of all death, cardiac death or non-fatal MI in comparison with BMS. The rates of death and MI were similar; do DESs have some other beneficial effects to reduce death and MI, thereby offsetting the risk of stent thrombosis? Despite general belief, the in-stent restenosis (ISR) is not quite a benign entity. The Cleveland Clinic experience with 1200 cases of single lesion bare metal ISR, underlined that 26,4% of

patients were presented with unstable angina, and 9,5% of patients with MI (7,3% NSTEMI and 2,2% STEMI). The need to repeat revascularization carried a risk of procedural deaths (8 cases – 0,7%) (15). The CRF analysis demonstrated that 86% reduction in restenosis at 1 year by using DES has been determined a significant 50% to 60% reduction in ischemic TLR and TVR throughout four-year period of follow-up. Subgroup analysis has been shown a 60-80% benefit across all lesion and patient subsets.

years, showing an early hazard for stent thrombosis among the bare-metal stent patients. Additional analyses are needed to evaluate the possible association with restenosis and subsequent revascularization procedures. This phenomenon may have been missed by previous studies, which excluded patients with repeat revascularization procedures who sustained later thrombosis events.

In conclusion, there is a clear signal that late stent thrombosis occurs more frequently with

Variables, 4 years FU	SES vs. BMS (n = 1748) CYPHER stent n = 870 BMS n = 878	PES vs. BMS (n = 3506) TAXUS stent n = 1748 BMS n = 1757
Freedom from all cause death	93,3% (57) vs. 94,8% (44), ns	93,4% (92) vs. 93,8% (86), ns
Freedom from cardiac death	96,5% (29) vs. 97,4% (22), ns	97,0% (42) vs. 97,6% (36), ns
Freedom from MI	93,6% (55) vs. 93,8% (53), ns	93,0% (110) vs. 93,7% (104), ns
Freedom from death and MI	88,4% (100) vs. 89,7% (88), ns	87,6% (186) vs. 88,2% (182), ns
Freedom from death or Q-wave MI	91,8% (70) vs. 93,7% (53), ns	92,5% (107) vs. 92,7% (105), ns
Freedom from stent thrombosis	98,8% (10) vs. 99,4% (5), ns	98,7% (20) vs. 99,1% (14), ns
Freedom from (per protocol) stent thrombosis After 1 year	5 vs. 0 , p = 0,025	9 vs. 2, p = 0,033
Freedom from ischemic TLR	92,2% (66) vs. 76,4% (202), p< 0,0001	89,9% (164) vs. 80,0% (337), p<0,0001
Freedom from ischemic TVR	87,9% (102) vs. 72,5% (235), p< 0,0001	83,0% (268) vs. 75,4% (408), p<0,0001

FIGURE 1. DES safety and efficacy in CRF meta-analysis

Moreover, the independent, intent-to-treat analysis by Harvard Clinical Research Institute (HCRI), which applied a new, broad consensus definitions developed by academic investigators, industry and regulators known as the Academic Research Consortium (ARC), demonstrated that the rate of any thrombosis from 0-4 years was 3,5 percent (29 patients from a pool of 832) for the CYPHER® Stent arm and 3,4 percent (28 patients from a pool of 825) for bare-metal stents. The ARC definitions for thrombosis (Figure 2) included definite, which required confirmation of thrombus on angiogram at follow up; probable, which included a MI in the treated vessel in patients who did not have an angiographic confirmation of a thrombosis; and possible, which included sudden unexplained death that could not be attributed to another cause, such as a car accident or cancer. These definitions were used to capture all possible adverse events that might be attributable to stent thrombosis and to thoroughly evaluate the long-term safety of potential treatments for coronary artery disease. The analysis was performed on the complete four-year data of 1,748 patients, the longest of

any drug-eluting stent, from the randomized clinical trials SIRIUS, E-SIRIUS, C-SIRIUS and RAVEL, all of which compared the CYPHER® Stent to bare-metal stents in the treatment of de novo coronary artery lesions. The data did demonstrate differences in the timing of the incidence of such events between bare-metal and drug-eluting stents. At no point throughout the four-year period were the differences significant. Analyses of sub-populations are ongoing. Thrombosis that was considered "definite or probable", a more specific assessment of the rates of thrombosis in the two treatment arms according to the ARC definitions, was 1.6 percent (13 out of 832 patients) in the CYPHER® Stent group and 1,7 percent (15 out of 870 patients) in the bare-stent arm from 0-4 years.

There is no difference versus bare-metal stents in the rate of thromboses at four years by either version of this standardized definition, providing the most appropriate information about the long-term safety of DES. The HCRI analysis of data based on the ARC definitions is also the first-ever comprehensive evaluation of thrombosis in bare-metal stents out to four

current DES than BMS, with a 0,2%-0,4% increase per year in the first 4 years. However, by using new ARC standardized definitions of stent thrombosis, the difference between DES and BMS in the rate of thrombosis does not seem significant.

Based upon available patient-level meta-analyses, the cumulative frequency of cardiac death and MI (the consequences of late stent thrombosis) are not significantly increased (though more data is needed, especially in "real-world" patients). The "breakthrough" success of DES in reducing restenosis and improving quality of life for patients with CAD should not become overshadowed by low event rate DES failures (i.e. late stent thrombosis).

The causes of late stent thrombosis are multifactorial and require the optimization of implantation technique and the identification of patients with aspirin/clopidogrel resistance. However, the majority of events are due to biological DES responses (delayed or incomplete endothelialization, abnormal flow pattern, etc.) and the major predictor of stent thrombosis is premature discontinuation of dual antiplatelet therapy. For the time being, the experts recommend extended dual antiplatelet regimen (1 year) for all DES patients, and possibly longer in special "high risk" situation such as bifur-

cation lesions, long diffuse lesions requiring multiple overlapping DESs, unprotected left main disease, chronic renal insufficiency or prior failed brachytherapy. The announced E-Select Registry and the INSIGHT Trial will evaluate standard vs. long duration clopidogrel in 30,000 patients with CYPHER® stents. The STENT Thrombosis Study will study the value of bed-evaluation of aspirin/clopidogrel responsiveness in 10,000 consecutive patients receiving DES, with a 2 to 5 years period of clinical follow-up. The PRO-TECT Randomized Trial will compare head-to-head 1st generation CYPHER® stent with 2nd generation ENDEAVOR® stent in 8,000 patients, having stent thrombosis as primary endpoint. BMS should be preferred to DES if extended dual antiplatelet therapy is problematic (planned surgery, poor compliance etc.). The risk-benefit ratio should be strongly considered in off-label cases, until the results of large scale randomized controlled trials are available.

Nevertheless, a better understanding of causative mechanisms of both early and late stent thrombosis is mandatory. New "safer" DESs are needed – with improved bioactive surfaces, new drugs and drug carriers – as well as new pharmacological approaches, more orientated to patient-related factors. ❑

Timing	
Acute stent thrombosis*:	0-24 hrs post
Sub-acute stent thrombosis*:	> 24 hrs-30 days post
Early stent thrombosis:	0-30 days post
Late stent thrombosis:	> 30 days-1 year post
Very late stent thrombosis:	> 1 year post
Definite/confirmed stent thrombosis	
Autopsy evidence or angiographic confirmed stent thrombosis is considered to have occurred if:	
1. TIMI flow is:	
a. Grade 0 with occlusion originating in the stent or segment 5 mm proximal or distal to the stent region in the presence of thrombus;	
b. Grade 1,2 or 3 originating in the stent or segment 5 mm proximal or distal to the stent region in the presence of thrombus	
AND at least one of the following criteria within 48 hours:	
• New onset of ischemic symptoms at rest (typical chest pain with duration > 20 minutes);	
• New ischemic ECG changes suggesting of acute ischemia;	
• Typical rise and fall in cardiac biomarkers (>2x ULN of CK).	
Probable stent thrombosis	
Probable stent thrombosis is considered to have occurred in the following cases:	
1. Any unexplained death within first 30 days.	
2. Irrespective of the time after the index procedure, any MI in the absence of any obvious cause which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis.	
Possible stent thrombosis	
Possible stent thrombosis is considered to have occurred with any unexplained death beyond 30 days.	

FIGURE 2. Expanded (ARC) stent thrombosis definition

REFERENCES

1. **Serruys PW, Kutryk MJ, Ong AT** – Coronary-artery stents. *N Engl J Med* 2006; 354:483-495
2. **Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A** – Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; 293:2126-2130
3. **Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, Messenger JC, Khanal S, Peterson ED, Bach RG, Krumholz HM, Cohen DJ** – Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* 2006; 113:2803-2809. Epub 2006 Jun 12
4. **Nordmann AJ, Briel M, Bucher HC** – Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* 2006; [Epub ahead of print]
5. **Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R; RAVEL Study Group** – Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesion**s**. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; 346:1773-1780
6. **Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE; SIRIUS Investigators** – Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; 349:1315-1323
7. **Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G; E-SIRIUS Investigators** – Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003; 362:1093-1099
8. **Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, Kuntz RE, Popma JJ, C-SIRIUS Investigators** – The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004; 43:1110-1115
9. **Schampaert E, Moses JW, Schofer J, Schluter M, Gershlick AH, Cohen EA, Palisaitis DA, Breithardt G, Donohoe DJ, Wang H, Popma JJ, Kuntz RE, Leon MB, SIRIUS, E- and C-SIRIUS Investigators** – Sirolimus-eluting stents at two years: a pooled analysis of SIRIUS, E-SIRIUS, and C-SIRIUS with emphasis on late revascularizations and stent thromboses. *Am J Cardiol* 2006; 98:36-41. Epub 2006 May 4
10. **Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, Russell ME** – TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation.* 2003; 107:38-42
11. **Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME; TAXUS II Study Group** – Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003; 108:788-794. Epub 2003 Aug 4
12. **Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, O'Shaughnessy CD, DeMaio S, Hall P, Popma JJ, Koglin J, Russell ME; TAXUS V Investigators** – Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA* 2005; 294: 1215-1223
13. **Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME; TAXUS-IV Investigators** – A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; 350:221-231
14. **Dawkins KD, Grube E, Guagliumi G, Banning AP, Zmudka K, Colombo A, Thuesen L, Hauptman K, Marco J, Wijns W, Popma JJ, Koglin J, Russell ME; TAXUS VI Investigators** – Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. *Circulation* 2005; 112:3306-3313. Epub 2005 Nov 14
15. **Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL** – Bare metal stent restenosis is not a benign clinical entity. *Am Heart J* 2006; 151:1260-1264

Address for correspondence:
Nicolae Florescu, University Hospital of Bucharest, 169 Splaiul Independentei, Bucharest, Romania
email address: clausflorescu@yahoo.com