DRUG ELUTING STENTS: DOUBTS AND CERTITUDES

E. Camenzind

***Cardiology Department, University Hospital, Geneva.**

Introduction

Percutaneous coronary intervention (PCI) has become the most frequently used method for myocardial revascularization [1]. Further the advent of coronary stenting has led to a significant decrease in complications after PCI, resulting in improved patient outcome [2]. However, restenosis has remained the Achilles' heal, the main and most frequent concern after successful PCI using stents with an overall incidence close to 30% [2,3].

The search for potent methods to control the restenotic process has led to the development of an 'oncological-approach' to restenosis using both radiotherapy [4] or chemical agent administered site-specifically [5]. Drug eluting stents (DES) were developed to improve site specific delivery characteristics and consisted of (1) a stainless steel backbone (2) a cytostatic drug and (3) a non-bioerodable polymer containing the drug and titrating its release to the surrounding tissues. Using these devices, also termed first generation DES (1stg-DES: CypherTM Cordis, Johnson and Johnson and TaxusTM Boston Scientific Corporation), incidence of in-stent restenosis (ISR) diminished by up to 75% [6,7].

The angiographic success lead to a quick expansion of the use of 1stg-DES in clinical practice and its use in the majority of coronary lesion subsets (e.g. de novo complex lesions, long lesions, small vessels) as well as to high-risk patients (multivessel angioplasty, patients with diabetes) [8,9].

Long-term clinical follow-up lead to the observation of a novel disease entity, late stent thrombosis (LST > 30 days after index procedure), following the deployment of 1stg-DES [10-12].

The understanding of the pathophysiology of in-DES late thrombogenesis is essential to estimate the clinical long-term relevance of this issue, known to be difficult to predict and grawed by a high mortality rate (>40%) [13]. Further-

more an in-depth understanding of this process may help to develop new stent technologies.

Pathophysiology of thrombosis

It has been postulated that the pathogenetic fundamentals leading to LST in-DES can be explained the Virchow triad that consists in: (1) an abnormal vessel wall lining (e.g. endothelium), (2) an abnormal blood-flow pattern (e.g. slow flow) and (3) altered blood constituents (e.g. increased blood thrombogenicity) [14-15].

The first two components of the above described Virchow triad are site-specifically induced by an intra-coronary inflammatory response to the DES. In fact histo-pathological data on coronary vessel response to 1stg-DES in humans suggest that there is a significant peri-strut inflammatory response with incomplete re-endothelialisation [16]. As compared to bare metal stents (BMS), intravascular ultrasound analysis after 1stg-DES has shown increased rates of luminal widening as described by late acquired stent malapposition (LASMA) of the stent struts to the vessel wall, associated in approximately one tenth of these cases with angiographically visible aneurysms [17,18]. Luminal vessel widening will induce local rheological changes as well as perturbed blood flow [19] and not surprisingly recently described as associated to LST, a further confirmation of the above described pathogenetic concept [20].

The last and third component of the Virchow triad is linked to multiple systemic factors, which can influence the pro-thrombotic state of an individual patient as dehydration, inflammatory state and reduced antiplatelet regimen [21-24].

Thus the persistent site specific inflammatory reaction associated with a delayed or no healing response is the 'primum movens' or local substrate leading to the chain of components described by the Virchow triad and finally triggering a thrombotic event [15,16]. The strong inhibition of the healing response allowed to obtain excellent angiometric results (e.g. angiography and IVUS) reflecting however at the same time a persistent risk of late thrombotic event [6,25]. The relationship between angiometrics and potential late clinical events is shown in Figure 1 using angiography and QCA as an illustrative example. With potent DES we observe a J-shaped curve relationship between late loss (LL) and clinical events: both negative and high LL are linked to an excess in clinical events. LST is rare (flatter arm of the J) and more likely to occur in the patient population with negative LL. Repeat revascularisation is frequent (steeper arm of the J) and occurs more often as the LL values increase. Therefore, the paradigm that predicates the use of angiography as a surrogate endpoint for clinical outcome is no longer valid in the setting of technologies inducing vessel wall widening and incomplete re-endothelialisation [26]. The nearly linear relationship between angiographic results and clinical events observed with BMS has been lost with the use of DES because of the absence of a complete vessel healing response [27].

We are realizing that excellent luminal results (e.g. negative LL) may predict worse clinical outcomes (J-curve) and thus the principles of therapeutics seem respected also for endovascular interventions: the more potent the treatment the stronger the adverse effect.

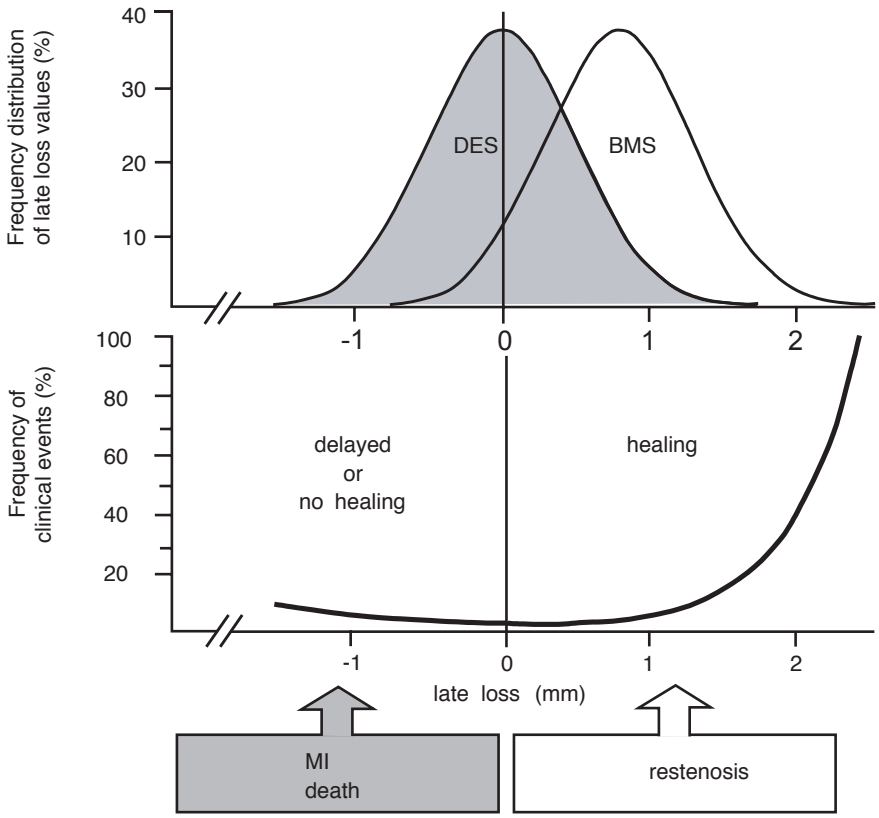

Fig. 1. J-curve relationship between late loss and clinical events: a negative late loss (left part of the frequency distribution curve) as well as increasing positive late loss (right part of the frequency distribution curve) are both linked to more clinical events. Rare events such as late thrombosis are more likely to occur in the population with a negative late loss (left arm of the curve) and more frequent events such as restenosis are more likely to occur with progressively increasing late loss (right arm of the curve). (modified from reference 15).

Clinical implications

Site-specific increased thrombogenicity favored by non-healing and thus both abnormal vessel re-endothelialisation and abnormal blood flow can be - at least partially - counterbalanced by the administration of dual antiplatelet therapy, which is usually maintained at least 3 to 6 months after 1st g-DES placement [6-9]. The importance of dual antiplatelet therapy is underscored by the finding that its interruption appears to be a potent correlate of LST, [10,12,13,28] a phenomenon already observed when stenting was associated with endovascular brachytherapy [29,30]. However prolonged dual antiplatelet therapy also increases bleeding risks [31,32] and costs, and causes problems when non-cardiac surgical or dental procedures are contemplated [10,12].

To estimate the group of patients at higher clinical risk of 'in-1st g-DES'

thrombogenesis and to assess the potential magnitude of the problem, one can focus on the patient population that has developed a site-specific, clinically recognizable pro-thrombotic factor e.g. luminal vessel widening. According to QCA, the proportion of cases below the 0 mm LL point - represented by the area under the negative part of the frequency distribution curve of LL values - is close to 50% (Figure 2) [33]. According to IVUS and the incidence of LA-SMA, the patient population at risk of LST after 1stg-DES can be estimated at 10% [17,18,34].

Noteworthy is that the shift to left of the frequency distribution curve is more pronounced in high-risk subgroups (e.g. diabetics) reflecting the fact that these subsets are more likely to develop a luminal widening [34,35]. This observation has been confirmed by serial IVUS analyses in diabetics in which LA-SMA was observed in 19.5% of the cases after DES as compared to 0% after BMS ($p<0.0001$) [34].

The fact that LASMA secondary to 1stg-DES is more frequent in patients with an increased risk of restenosis (e.g. diabetics) seems contra-intuitive, because some degree of resistance to the antiproliferative action of DES would be expected in patient/lesion subsets at higher risk for restenosis [34,35]. For the interventional cardiologist this makes the selection of patients in whom 1stg-DES should be implanted particularly difficult since the clinical benefit in terms of ISR reduction may be offset by an increased risk of LST that carries an unacceptably high morbidity and mortality [13].

Another site-specific criterion to evaluate vessel healing, may be 'stent coverage' as determined clinically by OCT [36]. A careful long-term observation of this parameter will be needed because the nature of stent coverage has not to be associated with reendothelialization and thus a coverage by a fibrin layer may not result clinically equivalent to endothelialization.

Results of clinical trials

In light of the above discussed site-specific and systemic mechanisms determining the patho-genesis of LST, the deployment of potent DES (e.g. 1stg-DES) is expected to be associated with the following pattern of clinical events in the late or non-healer population: (1) hard clinical endpoints as death and important MI secondary to LST, will continue to increase slowly but steadily over time (2) Revascularization rate will be low. However secondary to the increased long-term MI rate, a steady increasing frequency of direct PCI should be observed, which may appear as a slow progression of re-PTCA over-time and which may be influenced by the long-term interruption of dual antiplatelet therapy [28]. A further phenomenon that may influence late revascularization in DES is late restenosis also termed late catch-up. Interestingly this pattern could be demonstrated in a recent metaanalysis comparing two type of DES differing in the potency level: the potent 1stg-DES Cypher and the less potent Endeavor (Figure 3). How much of the observed late catch-up is due to restenosis and how much is due to re-PCI for MI remains to be evaluated.

Following BMS one is expecting during long-term follow up a lower incidence of hard clinical endpoint as death and MI because of a lower or absent incidence of LST. Revascularization rate will have an expected 6 to 9

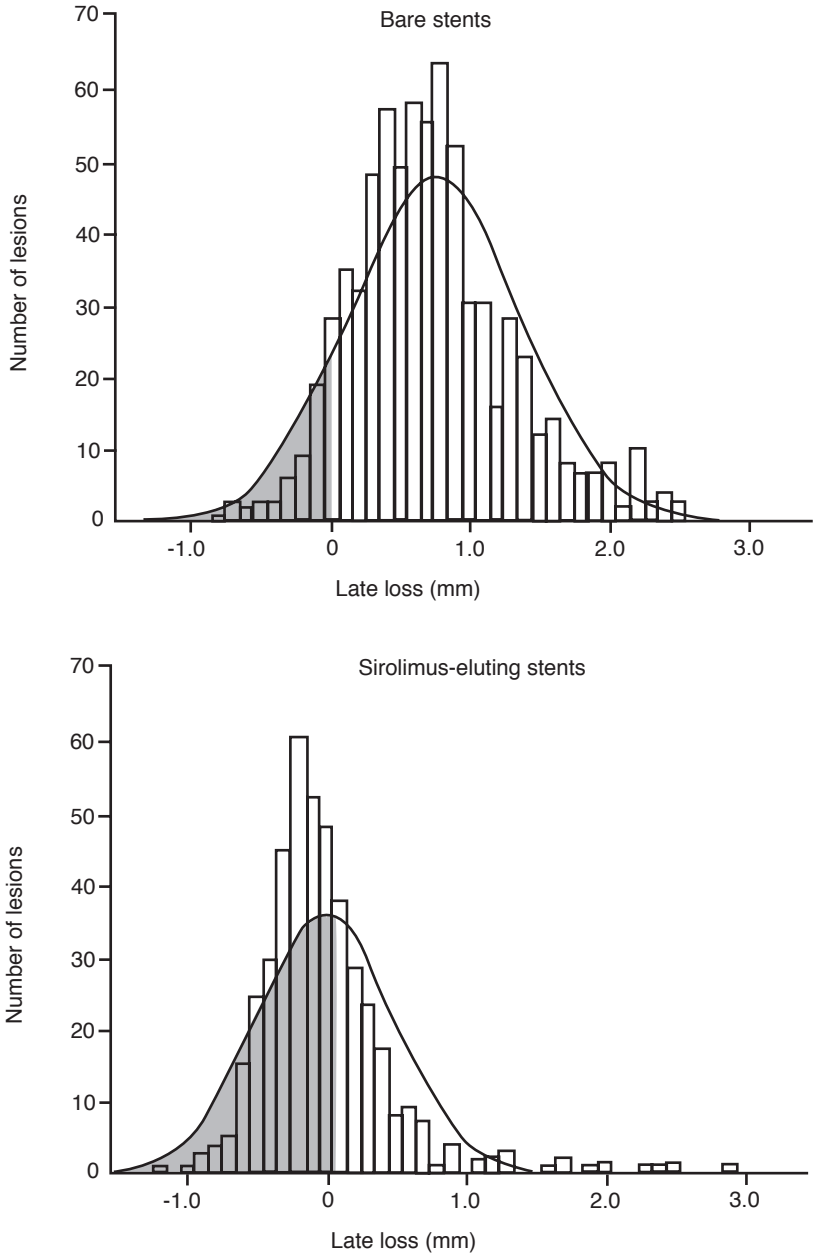

Fig. 2. Derived from the frequency distribution curve of the late loss (LL) values, the cases below the zero millimeter mark of LL represent the group having a positive vessel remodeling at follow-up. The area under the frequency distribution curve of LL below the zero millimeter mark represents therefore a collective of patients at risk of late stent thrombosis for having at least two criteria of the Vichow's triad (an abnormal vessel wall lining and an abnormal blood-flow pattern) (modified from reference 33).

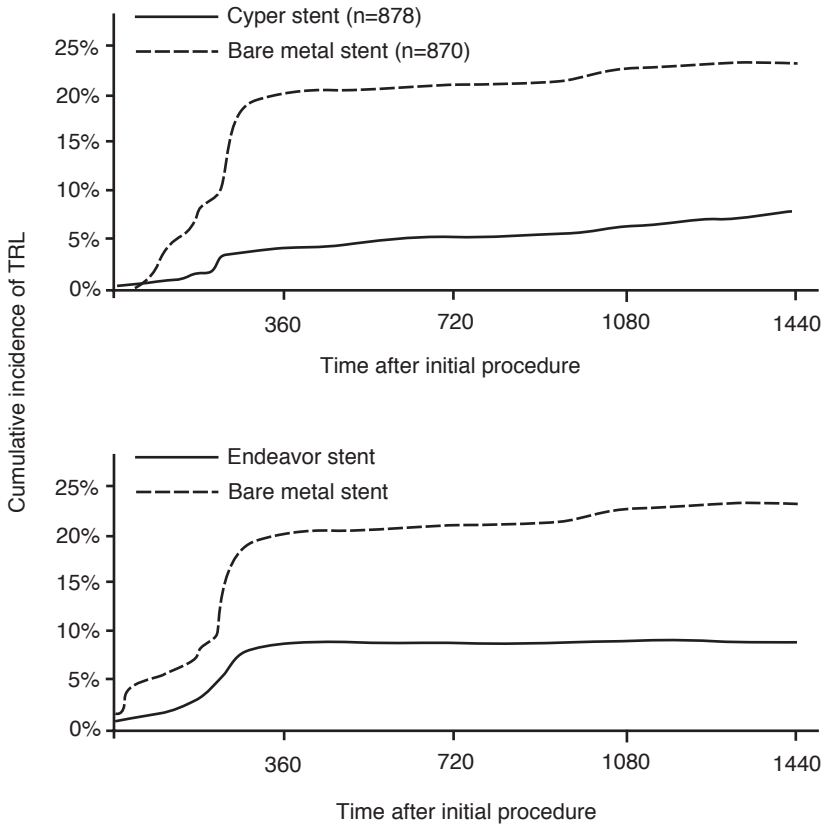

Fig. 3. Comparison of the long-term evolution of the cumulative incidence of total lesion revascularization (TLR) after two DES types with a different potency profile: a potent (CypherTM) and a less potent (EndeavorTM). Potent DES present an early (6-9 months) lower revascularization incidence which diminishes over time due to late catch–up and direct PCI secondary to acute MI. Less potent DES present a short-term higher revascularization incidence with a higher incidence of revascularization, however compensated by a more favorable long-term results.

months peak and its magnitude will be influenced by the type of follow-up (angiographic FU: higher re-PTCA rate; clinical FU: lower re-PTCA rate). This phenomenon was demonstrated elegantly in the Benestent II trial that showed a doubling of the re-PTCA rate after angiographic follow-up [37]. Further of interest is that late restenosis as mechanism is not expected after BMS but - if at all - a trend towards long-term luminal diameter improvement has been described [38].

Of importance is that these subtle long-term evolution patterns can only be observed in randomized trials. However even in randomized trials revascularization strategies (e.g. treatment modality for instent restenosis) may influence this subtle evolution pattern. If instent restenosis are systematically treated either with brachytherapy or potent DES the long-term BMS evolution pattern may be changed by this cross-over population.

The use of observational registries to compare long-term hard clinical endpoints between DES vs BMS should be avoided. The main reason why the incidence of death and MI will be difficult to compare is due to a main confounding factor: the influence of the physician's experience and knowledge to choose a specific treatment (BMS vs DES) for a given patient in a definite clinical setting. The physician's influence, which is evolvable in time, has been well documented in the SCAAR registry. The early data published in 2007 showed a relatively homogenous patient population treated either with DES or BMS in the period of 2003 and 2004 [39]. A comparison of DES vs BMS in this collective of patients showed an increased mortality and MI incidence in the DES group [39]. In a further analysis presented at the ESC 2007 entitled 'long-term outcome with drug eluting stents vs bare metal stents in Sweden – one additional year of follow-up', the investigators did not only show the long-term follow-up of the patient population enrolled between 2003 and 2004 but added also a more recent patient population treated during the year 2005 [40]. This added population made up for more than half of the total patient population (53%) and was not homogeneous any more concerning the indication of DES and BMS use as compared to the 2003 and 2004 collective. In this two years time period physicians had learnt to use DES for stable/unstable patients with a high cardiovascular risk profile (reflecting a high atherosclerotic burden and a potential increased risk of restenosis) and to use BMS for acute MI patients. Not surprisingly the mortality in the BMS group during the 2005 period was higher than in the DES group and it was higher than in BMS group of 2003 and 2004. When reflecting the influence of a different clinical indication, this increased mortality is expected to be more pronounced early. Of interest is that since Barcelona 2006 the use of observational registries to compare device performance has been frequently proposed to the medical world [41,42]. These comparative-registry evaluations show a very similar pattern: (1) an increased mortality in the BMS group, which was predominantly an early mortality and thus likely to reflect a selection bias. This 'selection bias' is secondary to an implementation of good clinical practice and a healthy common sense by the physician as elegantly shown in SCAAR. Thus patients at high procedural risk and with poorer prognosis (e.g. shock patient) were treated with technologies that are mechanically more performant and allowing shorter procedures as well as likely to show earlier healing and - last but not least - less costly. Further patient at high risk of bleeding or with a poorer long-term prognosis due to other diseases (e.g. neoplasia) were also likely to receive a BMS to avoid the need for a long-term dual antiplatelet regimen.

Independently of clinical evolution as death and MI one could focus on the incidence of stent thrombosis solely. The difficulty the physician is facing is to recognize what is meant by the term 'stent thrombosis'. In the literature stent thrombosis has been defined in different ways: the original per-protocol definition of early (< 30 dd) and late stent thrombosis (> 30 dd) has evolved to the academic research consortium (ARC) defined stent thrombosis. This later definition has defined three temporal categories (early [up to 30 dd], late [>30 dd-1year] and very late [>1 year]) and three levels of evidence (defined, probable and possible) [43]. The original article recommends the combination of adjudicated 'definite' and 'probable' ST to best characterize DES safety. 'Possible' ST inclu-

ding all death > 30 days after stent deployment was excluded [43]. A further subtle change included in the ARC definition is the recommendation to report all ST, including ST secondary to a reinterventions (e.g. brachytherapy or DES for instent restenosis). By doing so secondary ST will be attributed to the originally implanted device and from a ST pathogenesis point view the safety evaluation of the original device will be confounded. These definition changes of ST had an influence on both the frequency of reporting ST as well as on the distribution of ST in the BMS vs the DES group. Using the ARC definition a higher incidence of ST and a similar distribution of thrombotic events in both groups (DES and BMS) was reported [44]. When using the protocol definition a lower incidence of thrombotic events with a substantially higher incidence in the DES group could be observed [44]. Thus ST appears to be a very much definition dependent event.

Conclusions

For cardiologist, common practitioner and patient the understanding of the influence of changes linked to the modality of reporting data (e.g. from randomized trial to observational comparative registries) as well as linked to definition changes (e.g. stent thrombosis) is likely to be difficult to follow. This is particularly the case when we are confronted with contradictory results. We have learnt that there is the certitude that potent DES are likely to perform better according to angiometric parameters but clinically they left us with the doubt concerning long-term clinical safety. These doubts could not be completely erased by the suggested prolongation of dual antiplatelet regimen. Despite of this, the next future will be associated with measures of prevention of late thrombotic events and measures to determine potential safe and efficient indications for potent DES. In a farer future the adoption of new stents with better pro-healing characteristics will lead the field to more definite and clinically responsible solutions.

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