THIRTY-DAYS ONLY DOUBLE ANTIPLATELET THERAPY AFTER DRUG ELUTING STENTING: COULD A "SHORT-TERM" TREATMENT BE ADVANTAGEOUS?

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Abstract

The duration of Dual AntiPlatelet Therapy (DAPT) after coronary stenting has been evaluated in randomized studies with apparently conflicting results. Prolonged DAPT reduces late Stent Thrombosis (ST) and myocardial infarction, but at the expenses of more hemorrhages. Unluckily, bleedings are associated with higher morbility and mortality. Thus, in patients at high risk of bleeding the less effective Bare-Metal Stents (BMS) could be preferred to Drug-Eluting Stents (DES) due to the shortened DAPT needed. However, new DES technology carries a lower risk of ST and casts doubts on the recommended prolonged DAPT regimen after DES. Few studies with a low level of evidence already reported favorable results with short (<3 months) DAPT after DES. Notably, the LEADERS-Free trial has demonstrated that a polymer-free DES is superior to a BMS in elective patients at high risk of bleeding treated with a shortened (30 days) DAPT. Whether these seminal results could be replicated with durable or bioresorbable polymer-coated DES, or in different risk profile patients, like after acute coronary syndrome or with a lower bleeding risk, is of paramount importance since a shortened DAPT duration after DES could substantially reduce the risk of bleeding and improve prognosis.

Dual AntiPlatelet Therapy (DAPT) with aspirin and an ADP receptor antagonist is the foundation to prevent Stent Thrombosis (ST) and the duration of DAPT after coronary stenting has been extensively studied during the last decades [1]. Initially, patients were treated with a short course (15-30 days) of DAPT after Bare Metal Stenting (BMS). Afterward, Drug-Eluting Stents (DES) were approved on the basis of randomized trials (RCT's) in which DAPT was used for 3-6 months (only 2-months in the seminal RAVEL Trial) [1]. Few years

later, it was recognized that the tremendous restenosis benefit of DES was associated with a higher risk of Myocardial Infarction (MI) and death presumably due to late ST [2]. This 2.75 higher risk of late ST as compared to BMS was attributed to the delayed stent endothelialization of DES [1,2]. After this evidence, in 2006 the US Food and Drug Administration (FDA) consensus recommendation supported prolonged (at least 12 months) DAPT after DES implantation to prevent late ST, and this warning was rapidly incorporated in the International guidelines. However, this recommendation was not based on any prospective RCT's evidence. Unluckily, such prolonged DAPT enhances the risk of bleeding. Thus, in clinical practice where numbers of high bleeding risk patients are substantial, the less effective BMS are preferred in this setting due to the shortened DAPT regimen needed. However, several RCT's trials comparing prolonged and short DAPT therapy after implantation of mainly new generation DES have been planned during the last few years. These studies largely conclude that in stable patients a short-duration (3-6 months) DAPT results in similar rates of ST, MI, and death, but reduced bleeding risk, when compared to a longer (12-24 months) one [1,3]. Interestingly, a recent RCT's lowered the bar even further, and demonstrates that in patients at high risk of bleeding treated with a shortened (30-day) course of DAPT a polymer-free DES could offer better results than BMS stenting without increasing the risk of ST [4]. Thus, recent data highlights the increasing bleeding risk of patients after stenting and cast doubts on the cost-effectiveness of the former recommendation of routinely prolonging DAPT after DES.

The balance between the risk of bleeding and the risk of late stent thrombosis

Among patients undergoing PCI, it is estimated that 15% or more are at high risk for bleeding due to older age, comorbilities, needs of concomitant oral anticoagulants, or others [5]. Even in these cases prolonging DAPT after PCI reduces ischemic and thrombotic risk, but it carries an inherent risk of bleeding that increases further over time. Notably, in patients with stable vascular disease, or at risk of atherothrombotic events prolonged DAPT did not provide significant protection against ischemic events while it was associated with a significant 60% excess of moderate bleeding and a non-significant excess of severe or fatal bleeding complications [6]. Additionally, in the recent DAPT trial, extending clopidogrel from 12 to 30 months reduced ischemic events, but increased the relative risk of major bleeding by 56% versus placebo [7]. Furthermore, a recent meta-analysis demonstrated that for every ST event averted with longer DAPT, about 2 major bleeding are estimated to occur [8]. Moreover, all bleedings, whether they are insignificant, life threatening or fatal, may seriously affect morbility and mortality [5]. In fact, the Italian MANTRA Registry observed that unselected patients with Acute Coronary Syndrome (ACS) who bleed have a higher risk of death or MI, and these negative events occur few days after the hemorrhage [9].

Besides, 4-7% of patients undergoing PCI will require non-cardiac surgery in each year after the procedure and this need of surgery could force physicians to interrupt DAPT earlier [1]. Therefore, the identification of patients

deemed at risk of bleeding with prolonged DAPT duration is an important component of any PCI planning.

On the other hand, patients after PCI are at risk of coronary thrombotic events that can be classified as stent- and nonstent-related [10]. DAPT confers protection on both types of thrombotic events through suppression of platelet reactivity and aggregability. Physicians are particularly concerned of stent-related events in particular ST due to its association with a higher risk of MI and death. Not surprisingly, early cessation of DAPT has emerged as a strong, consistent, and independent risk factor for ST with BMS or first-generation DES. Thus, it could be easy to understand why in 2006 both FDA, and the cardiologic community rapidly recommended prolonged DAPT (at least 12 months) although at that time the level of evidence of such indication was below the accepted limits. Later on further studies observed that for some stable patient DAPT extension beyond 3 months confers no additional benefit in terms of reduction in ST, while it was associated with more bleedings [10]. These findings are not surprising since the pathophysiology of ST is multifactorial and could extend from patient-, to procedural-, or even stent-related factors. Luckily, a substantial improvement in stent endothelialization and strut thrombogenicity has been achieved with second-generation DES. Data from new technology DES (mainly with durable fluorinated polymer) show that the greatest risk of ST is within the first 30 days and that following this time frame this risk does not differ between patients on- or off-DAPT [11]. Thus, we may argue that better stent bioengineering with thinner struts, more biocompatible polymers, and more effective drugs could have affected the risk of ST with second-generation DES. Today, new technologic updates like abluminal drug coating, polymer-free or bioresorbable polymers, better elution of drug, or improvements in their anti-restenotic properties could offer further advantages and eliminate triggers for late or very late ST.

Finally, physicians should consider that from a clinical perspective thrombotic/ischemic and bleeding risks are not constant over time. In fact, while ST or recurrent ischemic events tend to peak early after PCI and substantially decrease or stabilize thereafter, the bleeding risk after a mild, early increase remains constant over time (fig. 1). Thus, finding the sweet spot between these opposed bleeding and thrombotic risk is of paramount importance at the time of PCI.

The LEADERS-FREE trial

In patients at high risk of bleeding current Guidelines favor the use of either a second-generation DES with a 3-6 months dual antiplatelet therapy or a BMS stent followed by 1 month of DAPT [12]. The latter strategy is associated with a higher risk of restenosis and re-intervention than that observed with the use of DES. These recommendation are the background of the LEADERS-FREE trial a randomized, double-blind study, that compared the umirolimus (biolimus A9)-coated, polymer-free and carrier-free stent with a very similar BMS in 2.466 patients with a high risk of bleeding who underwent PCI [4]. This high bleeding predisposition was mainly described by older age (65% of patients aged more than 75 years), and concomitant anticoagulation (35%). All patients received 1 month of DAPT, mainly clopidogrel. The primary safety endpoint, tested for both non-inferiority and superiority, was a composite of

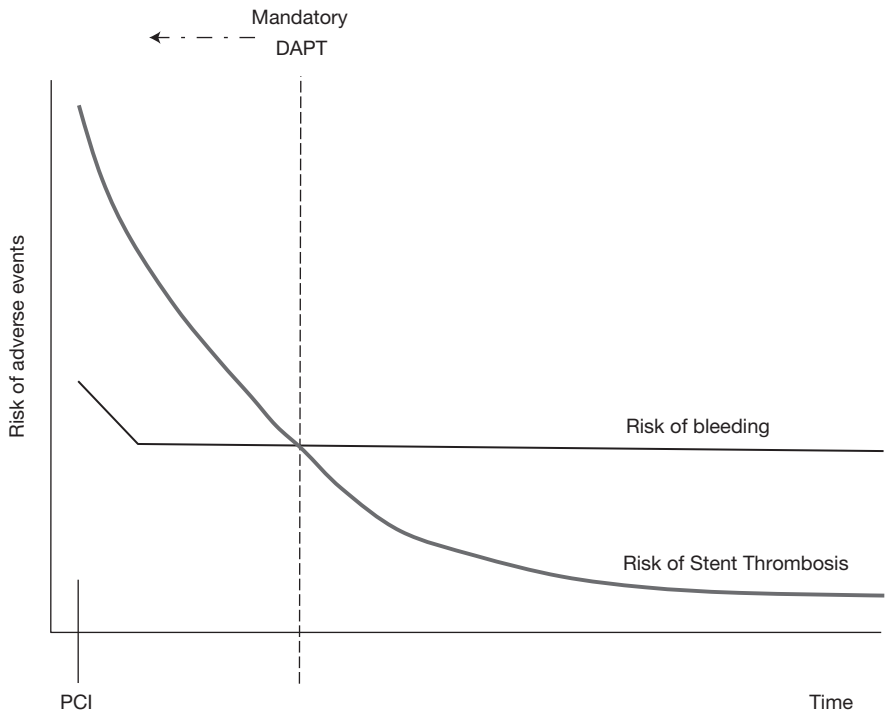

Fig. 1. Time-related differences between stent thrombosis and bleeding risk after stenting. Mandatory Double AntiPlatelet Therapy (DAPT) regimen represents the minimum time after PCI during which cessation of DAPT results in an unacceptably high risk for thrombotic events.

cardiac death, MI, or ST. The primary efficacy endpoint was clinically driven target-lesion revascularization. At 390 days, the primary safety endpoint had occurred in 112 patients (9.4%) in the polymer-free BA9-coated stent group and in 154 patients (12.9%) in the BMS group (estimated absolute risk difference, –3.6 percentage points; 95% confidence interval [CI], –6.1 to –1.0; P<0.001 for non-inferiority). This result was driven mainly by a lower rate of MI. At 390 days, the primary efficacy endpoint had occurred in 59 patients (5.1%) in the polymer-free BA9-coated stent group and in 113 patients (9.8%) in the BMS group [estimated risk difference, –4.8 percentage points; 95% Confidence Intervals (CI), –6.9 to –2.6; Hazard Ratio (HR), 0.50 (95% CI: 0.37-0.69) P<0.001] (fig. 2, panel A). Rates of definite or probable ST [polymer-free BA9-coated stent 2.0% vs BMS 2.2%, HR, 0.91 (95% CI: 0.53-1.59) P 0.75] were high in this study, and more than half the ST in both groups occurred during the first 30 days, when patients were still taking DAPT. The high rates of ST observed were impressive, although similar to those reported in other trials of unselected patients treated with DES, or in registries of triple therapy. However, these high rates of ST may be a consequence of the evenly high risk of bleeding among the patients enrolled that is associated with a higher risk for ST as well. In addition, the LEADERS-FREE trial included a pre-specified sub-study (LEADERS-FREE ACS) that addressed its ACS pop-

ulation, a true clinical challenge due to the imbalance of the opposing risks. Of these, 659 ACS patients were included in this analysis (polymer-free BA9-coated stent 330 patients, BMS 329 patients, respectively) [13]. At 12 month follow-up, treatment with the polymer-free BA9-coated stent was more effective (clinically driven target-lesion revascularization 3.9 vs. 9.0%, P=0.009) and safer (cumulative incidence of cardiac death, MI, or definite or probable ST 9.3 vs. 18.5%, P=0.001), driven by significantly lower rates of cardiac mortality (3.4 vs. 6.9%, P=0.049) and MI (6.9 vs. 13.8%, P=0.005) (fig. 2, panel B). These findings did not depend on the post-procedural DAPT scheme, the oral anticoagulation regimen, or imbalances at baseline. Thus, the LEADERS-FREE investigators provocatively concluded that in patients at high risk of bleeding the used of BMS should no longer be recommended since a second generation polymer-free DES offer superior results even in patients treated with a shortened (30-days) course of DAPT.

Other experiences

However, given the inherent limitation of this seminal study, these provocative conclusions of the LEADERS-FREE investigators should be reinforced by other data before their wide application in clinical practice. To date, few studies with a low level of evidence already reported favorable results with <3 months DAPT after DES. In a pooled population of patients receiving a Resolute Zotarolimus-Eluting Stent (R-ZES), where DAPT was prescribed for 6-12 months [14], the association between DAPT interruption and the rates of ST and major cardiac events was retrospectively analyzed. Three groups were identified: no interruption, interruption during the first month, and interruption between >1-12 months. There were 1.069 (21.8% of the pooled population)

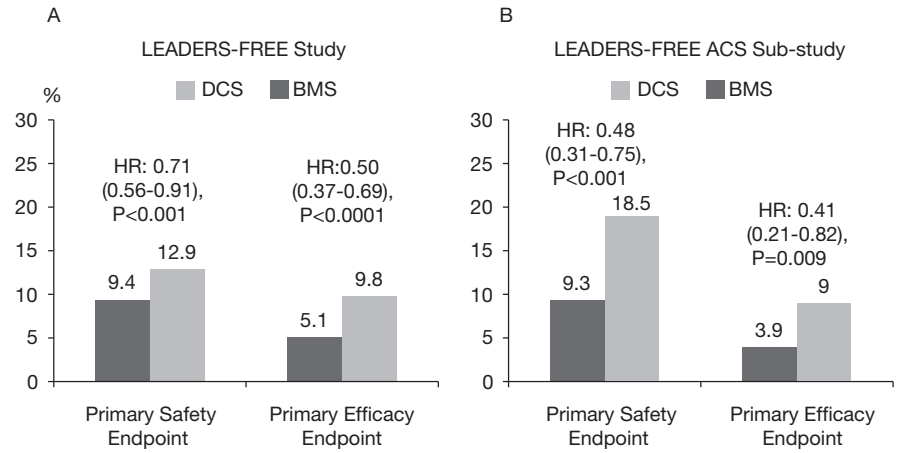

Fig. 2. Cumulative percentage of patients with the primary safety endpoint (a composite of cardiac death, myocardial infarction, or stent thrombosis), or the primary efficacy endpoint (clinically driven target-lesion revascularization). Panel A for the LEADERS-FREE Trial and Panel B for the LEADERS-FREE ACS Sub-study. Modified from ref. 5 and 12. DCS, Drug-Coated Stent, BMS, Bare-Metal Stent.

patients with a DAPT interruption and among the 166 subjects who interrupted therapy in the first month, 6 definite/probable ST events occurred (3.6%; all were long DAPT interruptions). Among the 903 patients in the >1-12 months (60% occurred between 6 and 12 months) interruption group, only 1 ST event occurred (0.1%; it was a 2-day long DAPT interruption). On the other hand, among patients with no DAPT interruption, 32 ST events occurred (0.8%). Rates of major cardiac events were 6.8% in the 1-month long interruption group, 1.4% in the 1-12 months interruption group, and 4.1% in patients that continued DAPT without interruptions. Thus, this sub-analysis showed that in second-generation DES, only DAPT interruptions within 1 month are associated with a high risk of ST or adverse outcomes, while DAPT interruptions between 1 and 12 months were associated with low rates of ST and adverse cardiac outcomes as well. Recently, Ariotti et al. [15] reported a prespecified analysis of the ZEUS trial, where 828 high bleeding risk patients were implanted with Endevour-Zotarolimus-Eluting Stent (E-ZES) or a thin-strut BMS and treated with a protocol-mandated 30 days DAPT regimen. The primary composite (death, myocardial infarction and target vessel revascularization) endpoint at 1-year occurred in 22.6% of E-ZES as compared with 29% of BMS patients [HR: 0.75 (95% CI: 0.57-0.98) p=0.033]. Again, definite or probable ST at 1 year occurred in 2.6% of E-ZES as compared to 6.2% of BMS patients (HR: 0.419, P=0.016). Thus, the author conclude that in patients at high risk of bleeding E-ZES as compared with conventional BMS followed by 30-days DAPT regimen provides superior efficacy and safety [15]. Interestingly, similar results has been reported by Kinnaird et al. [16], that compared 249 patients, operator-defined at high bleeding risk (mainly older age, anemia, and warfarin therapy) implanted with the polymer-free BA9-coated stent with a contemporary DES cohort. To note DAPT was prescribed for 3 months among polymer-free BA9-coated stent patients (56.7% for 30 days) as opposed to 12 months among the control DES group [16]. Thus, these preliminary data seem to support the use of shortened DAPT after new generation DES, but this results should be confirmed with adequately designed studies (tab. I).

Conclusions

Although the duration of DAPT after DES stenting has been extensively studied during the last decades, physicians still lack a firm "mandatory" duration of DAPT after new-generation DES [17]. Prolonged DAPT reduces late ST and MI, but at the expenses of more hemorrhages. Unfortunately, this could affect prognosis as well. Thus, in patients at high risk of bleeding the less effective BMS could be preferred to DES due to the shortened DAPT needed. However, new studies with a low level of evidence and a landmark RCT's trial question these recommendations. They suggest that new DES technologies carry a lower risk of ST that could allow a shortened (30 days) DAPT regimen after the procedure. Thus, it becomes an ethical must to define the minimum time after PCI during which cessation of DAPT results in an unacceptably high risk for thrombotic events. Beyond this timeframe, physicians need to go back to their clinical attitude and base the decision to continue or discontinue DAPT on an individual, clinical assessment of the trade-off between ischemic and bleeding risk.

Table 1 - Planned or on-going studies on shortened DAPT regimen after DES.

Trial	*Stent*	*Type of stent or coating*	*Limus kinetics*	*Patient population*	*Experimental arm DAPT*	*Control arm DAPT and type of stent*
SENIOR	Synergy EES	2nd generation bioresorbable polymer	Slow	1.200 elderly (>75 years) pts.	Stable CAD 1 month ACS 6 months	BMS, 1 month
YONSEI UNIVERSITY	BioFreedom drug-coated stent	Polymer-free	Fast	3.020 low risk stable CAD pts.	1 month	Biomatrix, 6-12 months
ISAR DAPT	Coroflex ISAR	Polymer-free matrix	Slow	906 low risk stable CAD pts.	3 months	6 months
REDUCE	Combo SES	EPC capture & bioresorbable polymer	Slow	1.500 low risk ACS pts. after successful PCI	3 months	12 months
ReCre8	Cre8 SES	Polymer-free	Slow	1.532 unselected pts	Stable CAD 1 month, ACS 12 months	R-ZES, Stable CAD 1 month, ACS 12 months
MASTER DAPT	Ultimaster SES	2nd generation bioresorbable polymer	Slow	4.300 high bleeding risk pts.	1 month	Guidelines
STOPDAPT-2	Xience EES	2nd generation durable polymer	Slow	3.000 low/med risk pts. successful PCI	1 month	12 months

DAPT: Dual AntiPlatelet Therapy; EES: Everolimus Eluting Stent; CAD: Coronary Artery Disease; ACS: Acute Coronary Syndrome; BMS: Bare Metal Stent; SES: Sirolimus Eluting Stent; EPC: Endothelial Progenitor Cell; PCI: Percutaneous Coronary Intervention; R-ZES: Resolute Zotarolimus.

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