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A critical review of evidence for safe dual anti-platelet therapy use in conjunction with second-generation coronary drug-eluting stent implantation

Introduction

In order to reduce the incidence of in-stent restenosis (ISR) after bare-metal stent (BMS) implantation, a new generation of stents was developed – drug-eluting stents (DES). The use of DES reduces restenosis and target vessel revascularization (TVR) by >70% compared with BMS.[1,2] Despite the success of DES in the treatment of coronary artery disease and the significantly lower incidence of ISR, doubts have arisen over the long-term safety and efficacy of these devices related to late adverse clinical events such as stent thrombosis (ST). In 2006, the results from the Basel Stent Cost-effectiveness-Late Thrombotic Events (BASKET LATE) study were presented. It was reported that after discontinuation of clopidogrel (between 7 and 18 months post-procedure), late stent thrombosis and related death/target vessel myocardial infarction (MI) events occurred twice as often with DES compared with BMS (2.6% vs 1.3%).[3] Data from early randomized clinical trials and meta-analyses using the standardized ST definition indicated that the risk of very late ST in patients persists at an annual rate of between 0.36% and 0.6% per year to at least five years after first generation DES implantation.[4] Questions arose as to whether the beneficial impact of DES on ISR outweighs the increased risk of late ST. As a consequence, new generations of DES have started to be developed.

It has been recognized that platelet activation, rather than the coagulation pathway, is responsible for ST.[5] Therefore, dual antiplatelet therapy (DAPT) with thienopyridine and aspirin became the standard of care after stent implantation. DAPT has been shown to reduce the risk of ST, MI complications, and death after DES placement.

The goal of this review is to describe the evidence for safe DAPT in conjunction with second-generation DES.

Overview role of DAPT and current agents used

In the past, the high incidence of ST was the main limitation of percutaneous coronary intervention (PCI) procedures. Over the years, many antithrombotic and antiplatelet drugs have been tested with the goal of decreasing the rate of ST (e.g., very high doses of aspirin,[6] dipyridamole in combination with aspirin,[7] warfarin with aspirin,[8] etc.). However, the use of some of these drugs resulted in higher incidences of haemorrhagic complications. The first positive results came with combined treatment using aspirin with thienopyridines.

The first thienopyridine was ticlopidine. In the STAR study, incidence of the combined endpoint (death, target vessel revascularization [TVR], angiographically evident thrombus or MI at 30 days) was 0.5% with aspirin plus ticlopidine, compared with 2.7% and 3.6% with aspirin plus warfarin and aspirin alone, respectively.[9] It was later shown that treatment with ticlopidine had its own complications (i.e., neutropenia, bone marrow attenuation, and haemolytic-uremic syndrome). Therefore, a new drug from the thienopyridine class – clopidogrel – was developed and has become standard in DAPT.

Clopidogrel is a prodrug requiring metabolic activation. It works by irreversible inhibition of the P2Y12 receptor, an adenosine diphosphate chemoreceptor on platelet cell membranes. The benefit of pretreatment with clopidogrel followed by DAPT with aspirin plus clopidogrel after BMS implantation in patients with non-ST-elevation acute coronary syndrome was assessed in the PCI-CURE study.[10] This study demonstrated a decrease in the primary endpoint (cardiovascular death or MI) in the group treated with DAPT for up to 1 year compared with the group treated for 2–4 weeks. The Clopidogrel for the Reduction of Events During Observation (CREDO) trial evaluated

the benefit of long-term (12-month) treatment with clopidogrel after elective PCI with BMS.[11] This trial revealed a 27% relative risk reduction in death, MI or stroke at 12 months. Nonetheless, clopidogrel has a number of limitations. It is a prodrug that requires metabolic activation and it also has a slow onset of action and presents widely variable inhibition of the platelet aggregation response.

A newer (third-generation) thienopyridine is prasugrel. This agent reduces the aggregation of platelets by irreversibly binding to P2Y12 receptors. Prasugrel inhibits adenosine diphosphate-induced platelet aggregation more rapidly and to a greater extent than standard or high doses of clopidogrel (fig. 1). It is important to note that prasugrel should not be given to patients after a stroke. In the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI 38), prasugrel was compared with clopidogrel in patients with moderate- to high-risk acute coronary syndromes who were scheduled for PCI with BMS or DES. The primary endpoint (cardiovascular death, non-fatal MI or non-fatal stoke) occurred in 12.1% of patients receiving clopidogrel and in 9.9% of patients receiving prasugrel (P<0.001).[12] In the TRITON-STENT sub-study,[13] treatment with prasugrel decreased the incidence of both early and late DES thrombosis (fig. 2).

After DES implantation, early ST was reduced in the prasugrel group compared with the clopidogrel group (0.42% vs 1.44%, respectively; P=0.0001). Similarly, late ST was significantly reduced in DES patients treated with prasugrel compared with those treated with clopidogrel after implantation (0.42% vs 0.91%, respectively; P=0.04). There was no difference in TIMI major bleeding between the two groups (2% vs 2%).

The next antiplatelet drug, ticagrelor, is an oral, reversible, direct-acting inhibitor of the P2Y12 receptor, which has a more rapid onset of action and is associated with more pronounced platelet inhibition than clopidogrel (fig. 3). This drug was assessed in the Platelet Inhibition and Patient Outcomes (PLATO) trial in patients admitted to the hospital with an acute coronary syndrome, with or without ST-segment elevation. At 12 months, the primary endpoint (a composite of death from vascular causes, MI, or stroke) occurred in 9.8% of patients receiving ticagrelor compared with 11.7% of those receiving clopidogrel (P<0.001).[14] Treatment with ticagrelor was associated with lower rates of death from vascular causes (P=0.001), as well as lower rates of death from any cause (P<0.001). No significant difference in the incidence of major bleeding events was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; P=0.43).

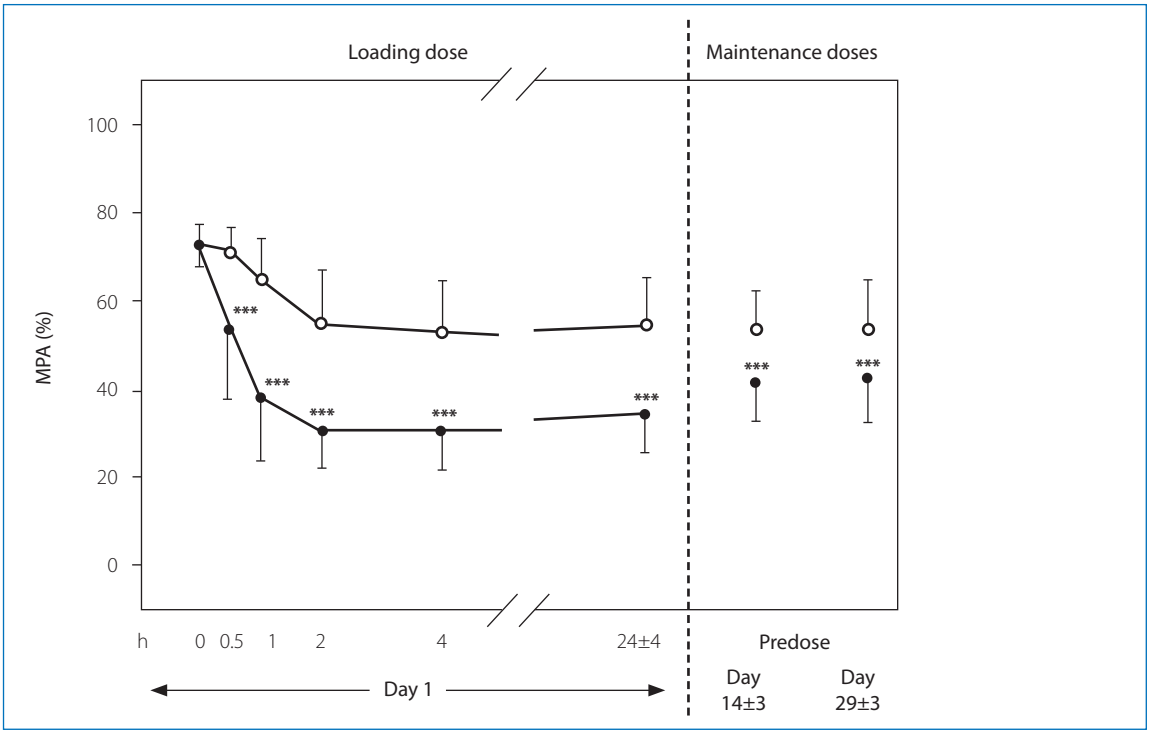
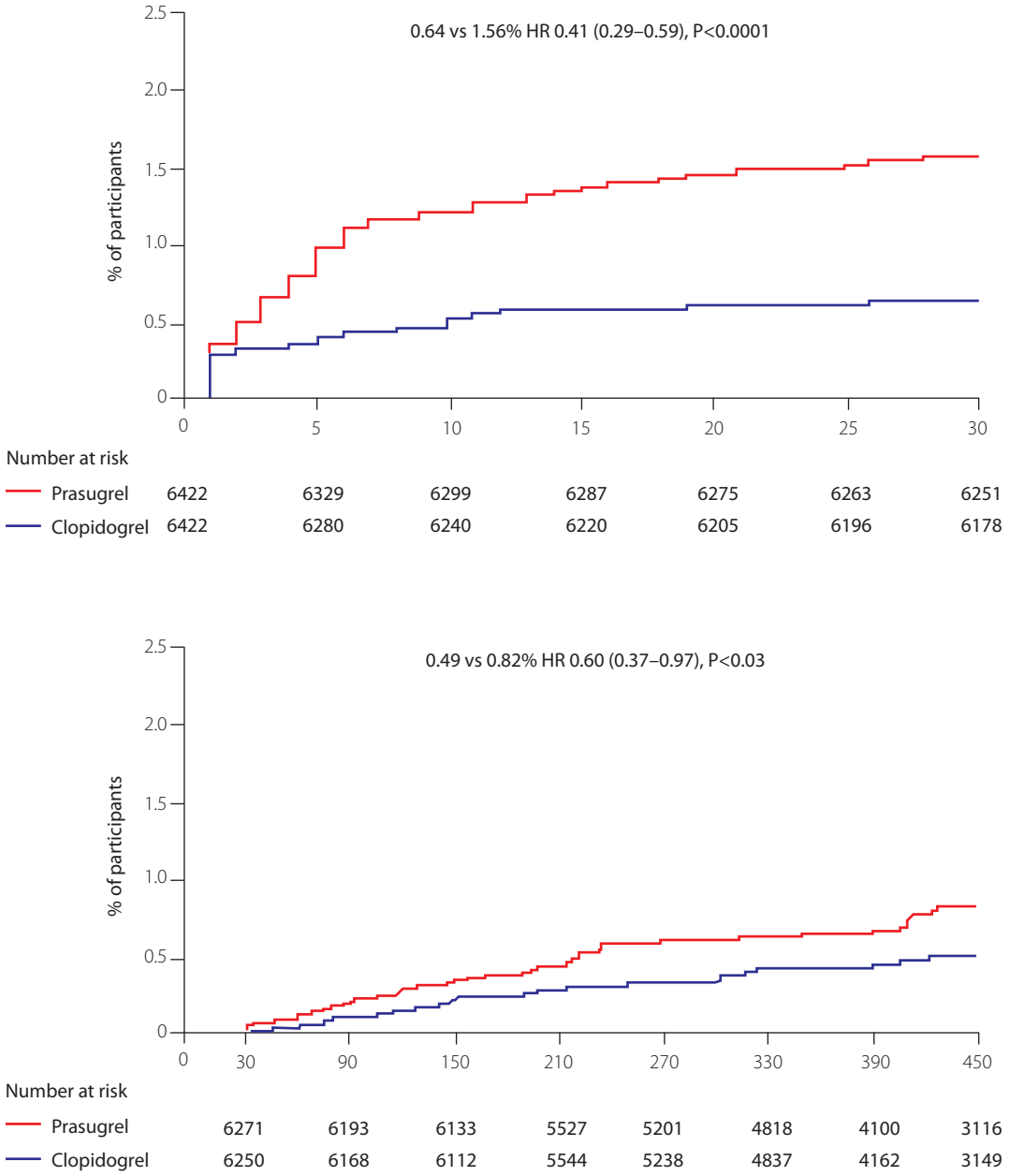


fig. 1

Maximal platelet aggregation (% MPA) induced by (20 μM) ADP over time following administration of prasugrel (60 mg loading dose [LD]/10 mg maintenance dose [MD]) and clopidogrel (600 mg LD/75 mg MD). Data presented as mean±SD. Closed circle represents prasugrel. Open circle represents clopidogrel. ***P<0.001 vs clopidogrel at the same time point.[60]

fig. 2

Kaplan–Meier curves of early (top) and late stent thrombosis using landmark analysis for all patients after DES implantation in the TRITON-TIMI 38 study.[13]



The first generation of DES

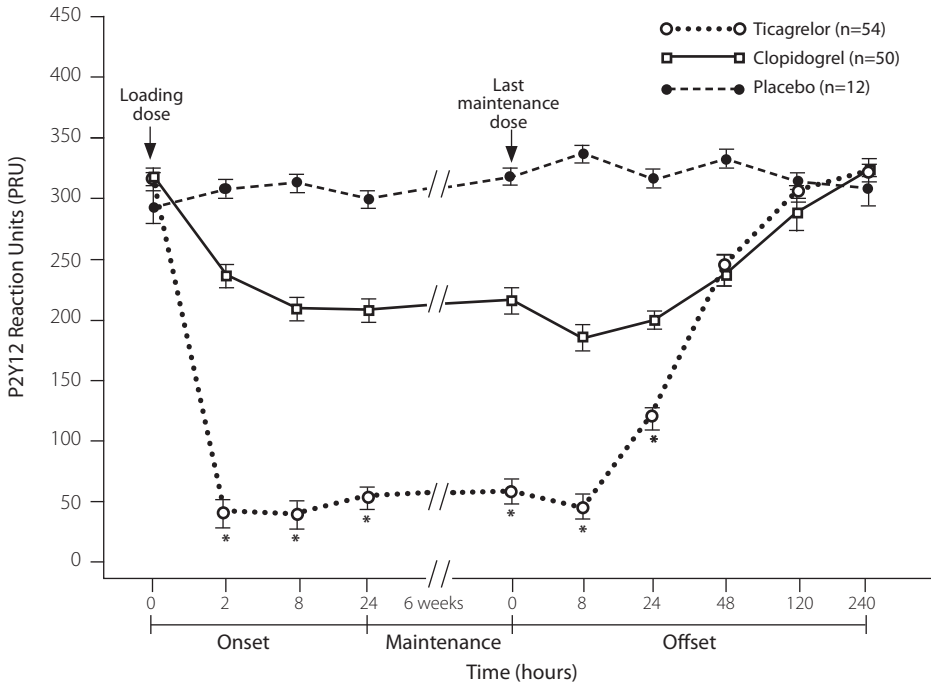
A DES consists of three components: a metallic stent platform, the active drug and a carrier for the drug. The active drug is released over time and inhibits the inflammatory process associated with healing of the arterial wall. The inhibition of restenosis by the active drug is mediated by its interference with the cell cycle in different ways.

First-generation DES substantially reduced the incidence of restenosis. The sirolimus- eluting stent (SES) Cypher® became the first DES to receive both European and FDA approval in 2002 and 2003, respectively. The efficacy and safety of the SES compared with BMS were investigated in five clinical trials (FIM,[15] RAVEL,[16] SIRIUS,[1] E-SIRIUS[17] and C-SIRIUS[18]). Results showed that use of the SES was associated with lower rates of ISR.

The next (first-generation) DES was the paclitaxel-eluting stent (PES) – TAXUS® Express2®. Its safety and efficacy were evaluated and established in the TAXUS I,[19] II[20] and IV[2] clinical trials. The TAXUS® Liberté® PES was assessed in the TAXUS ATLAS

fig. 3

P2Y12 reaction units (PRU) as assessed by the VerifyNow P2Y12 assay by protocol time and treatment. Data are expressed as mean±SEM. *P<0.0001, ticagrelor vs clopidogrel.[61]



trial. It was found to be non-inferior to the TAXUS® Express2®, with similar rates of ISR and TVR at nine months.[21] The duration of clopidogrel administration was determined by the duration of active drug release from the stents, which was two months for SES and six months for PES.

Late stent thrombosis

After the initial enthusiasm for DES, their use in clinical practice had become ubiquitous, but concerns began to arise about long-term safety. Therefore, a number of large-scale meta-analyses were performed to assess both the short- and long-term safety of DES relative to BMS.[22-24] Results of these studies showed no increase in mortality between patients receiving DES and those receiving BMS. In 2007, a standard definition of ST was proposed by the Academic Research Consortium (ARC).[25] This definition categorizes ST according to the degree of documentation and its timing (i.e., definite, probable or possible). Based on the elapsed time since stent implantation, ST is classified as early (0–30 days, including acute and subacute), late (>30 days, <365 days) and very late (>12 months).

Using this definition, a pooled analysis of long-term follow-up from eight clinical trials, including the CYPHER® SES and TAXUS® Express2® PES, was performed. Data from the analysis showed similar rates of early and late ST. However, a higher incidence of very late ST was reported with DES (after one year, there were five episodes of ST in patients with SES compared with no episodes in patients with BMS [P=0.025] and nine episodes in patients with PES compared with two episodes in patients with BMS [P=0.028]).[26] The risk of very late DES thrombosis was confirmed in a meta-analysis of eight clinical trials. The incidence of very late ST was 5.0 events per 1,000 DES patients, with no events in BMS patients (risk ratio: 5.02, 95% confidence interval: 1.29–19.52; P=0.02).[27] Late ST was found to be associated with clinical factors such as acute coronary syndrome, diabetes mellitus, renal failure, low ejection fraction, aspirin or clopidogrel resistance and with angiographic features such as bifurcation lesions, small vessels and total stent length. However, the most important risk factor for late ST was premature discontinuation of antiplatelet therapy.[3,28,29] All these data supported the use of DAPT for at least one year after DES implantation, as recommended by the ACC/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines,[30] and emphasized the importance of continuing DAPT, without interruption, for a full year after DES implantation.[31]

The second and third generations of DES

During the following years, research focused on the development of novel permanent or bioabsorbable

DES that release newer antiproliferative drugs and on stents containing carrier systems with bioabsorbable polymers or polymer-free DES – second– and third-generation DES. First-generation DES had metal scaffolds made from stainless steel, while second-generation coronary stents are made with cobalt chromium struts. Cobalt chromium has an advantage over stainless steel: it is more radiopaque, it has more radial force, and it is thinner.[32] There is an association between stent strut thickness and restenosis (at least with regard to bare metal stents made of stainless steel), with thinner struts associated with less restenosis.[33]

The Endeavor® stent utilizes a phosphorylcholine polymer to deliver a sirolimus analog, zotarolimus (zotarolimus-eluting stent; ZES). Its safety and efficacy were established in the non-randomized ENDEAVOR I FIM trial.[34] The first randomized clinical trial comparing ZES to BMS showed that the rates of binary in-stent restenosis and TVR remained significantly lower with the ZES compared with the BMS at both eight and nine months. Incidence of ARC-defined 'definite' and 'probable' very late ST remained low (0.2% ZES and 0.3% BMS) through to five years.[35] Two randomized trials were designed to show that ENDEAVOR ZES was as effective as the CYPHER® SES (ENDEAVOR III) and the TAXUS® Express2® PES (ENDEAVOR IV). In the ENDEAVOR III trial, ZES were associated with more in-stent late loss, binary ISR and TVR at nine months.[36] However, after five years, patients who received a ZES had a lower incidence of all-cause mortality, MI and major adverse cardiac events (MACE). There was no difference between ZES and SES in target lesion revascularization or ST at five years.[37] The ENDEAVOR IV trial showed no difference in vessel revascularization, cardiac death, MI or ST at 12 months (clopidogrel was dosed at 75 mg daily for at least six months).[38] The efficacy and safety of the ENDEAVOR ZES versus CYPHER® SES in a routine clinical setting with no direct follow-up was assessed in the SORT-OUT III superiority trial.

At nine months, the primary endpoint had occurred in 6% of patients in the ZES group compared with 3% in the SES group (P=0.0002). At 18-month follow-up, this difference was sustained (10% vs 5%; P<0.0001).[39] At 3-year follow-up, the very late definite ST occurred in no patients in the ZES group versus 12 (1.1%) patients in the SES group (P=0.0005).[40]

The next approved second-generation DES was the Xience V® (Abbott). It is an everolimus-eluting stent (EES) with a biocompatible polymer and a synthetic derivative of sirolimus, everolimus. The safety and efficacy of EES were assessed in the first SPIRIT trial.[41] Results showed lower in-stent late loss (0.1 mm vs 0.87 mm, P<0.001) and binary ISR (0% vs 25.9%; P<0.01). The SPIRIT II trial evaluated the safety and performance of the Xience V® EES compared with the TAXUS® PES. All patients enrolled in this study received clopidogrel at 75 mg daily for a minimum of six months after the index procedure. At six months, the in-stent late loss was 0.11 ± 0.27 mm in the EES arm compared with 0.36 ± 0.39 mm in the PES arm (P<0.0001), and there was no significant difference between groups in the rates of MACE.[42] At the three-year follow-up, the rate of ST was low in both groups (EES: 1.0%; PES: 2.9%).[43] The SPIRIT III trial enrolled 1,000 patients who were randomized 2:1 to receive the EES or PES. In-stent late lumen loss was significantly less in patients who received an EES compared with those who received a PES (0.14 mm vs 0.28 mm; P<0.004). There were also significant reductions in the composite MACE endpoint at one year (6.0% vs 10.3%; relative risk, 0.58 [95% CI: 0.37–0.90]; P=0.02).[44] The superiority of EES over PES in terms of clinical endpoints was assessed in the SPIRIT IV trial. In SPIRIT IV, the incidence of the combined primary endpoint (cardiac death, target-vessel MI, or ischemia-driven TVR) was 4.2% at one year in EES patients compared with 6.8% in PES patients (P=0.001). Additionally, the one-year rates of ST were lower with EES (0.17% vs 0.85%; P=0.004).[45] The comparison of EES with PES in real-life practice was evaluated in the COMPARE study[46] and yielded the same results as the SPIRIT IV trial. The Efficacy of Xience/promus Versus CYPHER® in Reducing Late Loss after Stenting (EXCELLENT) trial compared the Xience/Promus EES with the CYPHER® stent. The primary endpoint (in-segment late loss at nine months) was 0.11 ± 0.38 mm and 0.06 ± 0.36 mm for EES and SES, respectively (non-inferiority P=0.0382). The incidence of clinical endpoints was not statistically different between the two groups.[47]

One of the newer permanent polymer-coated DES is the Endeavor® Resolute ZES (R-ZES), which is based on a Driver cobalt-chromium BMS coated with a formulation of zotarolimus and a polymer referred to as Biolinx (a blend of three different polymers), which allows delayed drug release. At least 85% of the zotarolimus is released within 60 days, with the

table 1

Clinical trials with different DES.

Clinical trials	Number of patients	Stents	Primary endpoint	Result	P value	Minimal duration of Clopidogrel treatment (months)
SIROLIMUS						
FIM	30	Cypher SES	Safety and efficacy of two different formulations of SES: in-stent late loss	Slow-release SES 0.09 mm Fast-release SES -0.02 mm	NA	2
SIRIUS	1,058	Cypher SES x BMS	Target vessel failure	SES 8.6% x BMS 2.1%	<0.001	2
C-SIRIUS	100	Cypher SES x BMS	In-stent minimal lumen diameter	SES 2.46mm x BMS 1.49mm	<0.001	2
E-SIRIUS	352	Cypher SES x BMS	Minimum lumen diameter	SES 2.22mm x BMS 1.33mm	<0.001	2
RAVEL	238	Cypher SES x BMS	Mean late loss	SES 0mm x BMS 0.8mm	<0.001	2
PACLITAXEL						
TAXUS I	61	TAXUS PES x BMS	MACE rate	PES 3% x BMS 10%	0.612	6
TAXUS II	536	TAXUS PES x BMS	In-stent net volume obstruction	Slow-release PES 6.9% x Fast-release PES 7.8% x BMS 23.2%	<0.0001	6
TAXUS IV	1,314	TAXUS PES x BMS	Ischaemia-driven target-vessel revascularization	PES 4.7% x BMS 12%	<0.001	6
TAXUS ATLAS	871	TAXUS PES x TAXUS Liberté	Non-inferiority of TAXUS Liberté versus TAXUS Express	TAXUS PES 7.01% x Liberté 7.95%	0.0487	6
ZOTAROLIMUS						
ENDEAVOR I	100	Endeavor ZES	Safety and feasibility of the Endeavor stent	30-day rate of adverse clinical events 1%	NA	X
ENDEAVOR II	1,197	Endeavor ZES x BMS	Target vessel failure	ZES 7.9% x BMS 15.1%	<0.0001	3
ENDEAVOR III	436	Endeavor ZES x Cypher SES	In-segment late lumen loss	ZES 0.34 mm x SES 0.13 mm	<0.001	3
ENDEAVOR IV	1,548	Endeavor ZES x TAXUS PES	Non-inferiority of nine-month target vessel failure	ZES 6.6% x PES 7.1%	<0.001	6
First-in-human	139	Endeavor Resolute ZES	In-stent late lumen loss	R-ZES 0.22 mm	NA	6
RESOLUTE All-comers	2,292	R-ZES x EES	Target lesion failure	R-ZES 8.2% x EES 8.3%	non-inferiority P<0.001	6
RESOLUTE US	1,402	R-ZES x Endeavor ZES	Target lesion failure	R-ZES 3.7% x E-ZES 6.5%	non-inferiority P<0.001	12
TWENTE	1,391	R-ZES x XIENCE-V EES	Target vessel failure	R-ZES 8.2% x EES 8.1%	non-inferiority P=0.001	12
EVEROLIMUS						
SPIRIT FIRST	60	XIENCE-V EES x BMS	In-stent late loss	EES 0.1 mm x BMS 0.87 mm	<0.001	X
SPIRIT II	300	XIENCE-V EES x TAXUS PES	In-stent late loss	EES 0.11 mm x PES 0.36 mm	<0.0001	6
SPIRIT III	1,002	XIENCE-V EES x TAXUS PES	In-stent late loss	EES 0.14 mm x PES 0.28 mm	< or =0.004	6
SPIRIT IV	3,687	XIENCE-V EES x TAXUS PES	Target lesion failure	EES 4.2% x PES 6.8%	<0.001	6

remainder being released within 180 days. The safety and efficacy of the R-ZES was tested in a feasibility study. The R-ZES demonstrated low in-stent late lumen loss, low target lesion revascularization and no ST during a 12-month follow-up.[48] The R-ZES was compared to the Xience V® stent in the RESOLUTE All-Comers trial.[49] At the 12-month follow-up, the R-ZES was non-inferior to EES with respect to the primary clinical endpoint of target lesion failure (TLF), defined as a composite of death from cardiac causes, any MI, or clinically indicated target lesion revascularization (R-ZES: 8.2% vs EES: 8.3%, non-inferiority P<0.001). The two-year outcomes from the RESOLUTE

All-Comers trial were published in 2011. The patient-related outcome (all deaths, MI, and revascularization) occurred equally in both groups (R-ZES: 20.6% vs EES: 20.5%). Similarly, stent-related events occurred in 11.2% of patients who had received R-ZES vs 10.7% of patients who had received EES. Three patients in each group (0.3%) had a very late ST.[50] A prospective observational study, which evaluated the clinical effectiveness of the R-ZES, was performed in United States. In this study, 1,402 patients with a mean reference vessel diameter of 2.59 ± 0.47 mm were enrolled; diabetes prevalence in the study population was 34.4%. In the main analysis cohort (2.5–3.5 mm stents and single-lesion treatment), TLF was 3.7% at 12 months compared with historical Endeavor® ZES results (6.5%; non-inferiority P<0.001). The overall TLF rate was 4.7% and rates of cardiac death, MI, and target vessel revascularization were 0.7%, 1.4%, and 2.8%, respectively. The 12-month rate of ST was 0.1%. DAPT use was 97% at 30 days and 93.3% at 12 months. Definite or probable ST was observed only among patients treated with 2.25 mm stents.[51] A comparison between the R-ZES and the Xience V® EES in patients with advanced coronary disease and complex lesions in a real-world setting was performed in The real- World Endeavor Resolute versus Xience V Drug-eluting Stent Study in Twente (TWENTE) trial. Target vessel failure (TVF) occurred in 8.2 and 8.1% of patients who had received R-ZES and EES, respectively (non-inferiority P<0.001). Definite ST rates were low (0.58 and 0%; P=0.12).[52]

DAPT with the new generations of DES

The optimal or minimal necessary duration of DAPT after DES implantation remains uncertain. Moreover, it has been a long time since a randomized trial was performed to compare shorter duration DAPT (<12 months). The pooled analysis of the underpowered REAL-LATE and ZEST-LATE trials evaluated the effect of extended DAPT beyond 12 months on long-term clinical outcomes in patients who underwent PCI with DES. The analysis showed no significant benefit associated with clopidogrel continuation beyond 12 months compared with clopidogrel discontinuation at 12 months, relative to a reduction in the incidence of death or MI for patients who had received DES (i.e., zotarolimus-, sirolimus-, or palcitaxel-eluting stents). The ST rate after 23 months was the same with DAPT that was discontinued at 12 months and with DAPT that was extended beyond 12 months.

In 2012, data from the prospective, multi-centre EXCELLENT trial were published. In total, 1,443 patients were randomly assigned to either 6- or 12-month DAPT after receiving sirolimus or everolimus DES. Six months of DAPT was found not to be inferior to 12 months of DAPT relative to the risk of TVF (6-month DAPT: 4.8% vs 12-month DAPT: 4.3%; non-inferiority P=0.001). ST tended to occur more frequently in the 6-month DAPT group compared with the 12-month DAPT group (0.9% vs 0.1%; P=0.1). In the EES group, the primary endpoint occurred in 4.72% and 4.94% of patients in the 6– and 12-month DAPT groups, respectively. After EES implantation, the incidence of ST was 0.6% (6-month DAPT) and 0.2% (12-month DAPT; no significant difference between groups). All patients in the EES group were taking both aspirin and clopidogrel at the time of ST. Bleeding rates were not significantly different between the two groups, although bleeding was numerically at least twice as frequent in the group receiving 12-month DAPT than in the group receiving 6-month DAPT (0.6% vs 1.7%).[53]

In the Prolonging Dual Antiplatelet Treatment After Grading Stent-induced Intimal Hyperplasia study (PRODIGY), all-comer patients with an indication for coronary stenting were randomly treated (balancing randomization) with BMS, TAXUS®, Endeavor® and Xience V®. At 30 days, patients in each stent group were randomly allocated to receive clopidogrel therapy for 24 months or for up to 6 months. At two years, there was no difference in the primary endpoint (death, MI, stroke) between 6-month and 24-month DAPT (10% vs 10.1%). Prolonged DAPT after DES implantation did not reduce the rate of late and very late ST (P=0.80 for the difference in definite ST between 6- and 24-month DAPT). As might be expected, the bleeding risk was significantly increased with 24-month DAPT (3.5% and 7.4% for 6- and 24-month DAPT, respectively; P=0.00018).[54]

Safety outcomes relative to DAPT duration in patients treated with second- generation DES were studied in an analysis of five trials with ZES. In the multivariable analysis, 6-month DAPT was not associated with an increased likelihood of thrombotic events compared with extended DAPT at the three-year follow-up.

During the last couple of months some new data appeared regarding the 3-month duration of DAPT after implantation of modern last generation DES.

These data were not published until now and must be confirmed in randomized clinical trials. However, European Society of Cardiology (ESC) guidelines on myocardial revascularization recommend DAPT for 6–12 months after DES implantation in all patients, and emphasized the importance of avoiding discontinuation of DAPT during the first year after DES implantation.[55]

Risk associated with early DAPT discontinuation

Early discontinuation of DAPT has been identified as a risk factor for ST in patients with DES.[28, 29] ACC/AHA/SCAI guidelines for PCI state that patients should be counselled on the need for and risks of DAPT before placement of intracoronary stents, especially DES, and that alternative therapies should be pursued if patients are unwilling or unable to comply with the recommended duration of DAPT.[56] All these recommendations were made in the era of first-generation DES. The recommendations are based on data from registries and represent an expert consensus. Second-generation DES have a safer profile and lower risk of ST due to earlier intimal coverage. Angioscopy studies associated with ZES (Endeavor®) have shown neointimal stent coverage at the 3-month follow-up.[57] As mentioned above, the rates of ST linked to second-generation DES remain low.

Recent results from two randomized clinical trials have shown no benefit of extending clopidogrel treatment beyond six months.[53, 54] Additionally, prolonged DAPT is associated with significantly increased bleeding risks.

The most important issue prior to DES implantation is patient selection. Before deciding on PCI with DES, factors such as patient compliance, risk of major bleeding and foreseeable surgical procedures, which might require discontinuation of antiplatelet therapy, must be assessed.[58] Difficult decisions regarding DAPT arise when a patient who is receiving aspirin and a P2Y12 antagonist is required to undergo surgery that cannot be postponed. For such a situation, there is no universal recommendation. Aspirin should be continued if possible. If discontinuation of clopidogrel therapy is necessary, a P2Y12 antagonist should be resumed if there is adequate haemostasis after 24 hours post-surgery. In patients who require a temporary interruption of aspirin, clopidogrel, or both before surgery, it is recommended to stop this treatment at least five days (and preferably ten days), prior to the procedure. Continuation of DAPT is justified if the risk of ST outweighs the risk of procedure-associated bleeding. For patients receiving DAPT with excessive or life-threatening peri-operative bleeding, transfusion of platelets and administration of other pro-haemostatic agents is recommended.[59]

Conclusion

The new generation of DES using a novel platform (cobalt-chromium thin strut), highly biocompatible polymers and innovative antiproliferative drugs provide better outcomes with respect to in-stent restenosis and subsequent revascularization over DES from the first generation. Currently, development is focused on further improving the efficacy of DES. The long-term safety of newer generations of DES has been established in a number of randomized clinical trials. Second-generation DES (especially the everolimus- and zotarolimus-eluting stents) appear to be safe in the long term, at least comparable to BMS.

The use of DAPT with stents has significantly improved outcomes in patients undergoing PCI with stent implantation. The ESC Guidelines on myocardial revascularization provide practical guidance for current use of DAPT in the clinical setting, and recommend 6–12 months of DAPT after DES implantation in all patients; furthermore, they emphasize the importance of avoiding discontinuation of DAPT during the first year after DES implantation. Some patients may not tolerate or comply with DAPT for the requisite treatment period and may, therefore, be unsuitable for implantation with DES. However, new, more effective antiplatelet drugs now available for use in clinical practice are providing benefits to an increasing number of patients.

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