Dual antiplatelet therapy after drug-eluting stent implantation: long-term, short-term, tailored or related to stent type?

Doble antiagregación plaquetaria luego del implante de *stent* farmacológico: ¿por largo o corto tiempo, a medida o relacionada con el diseño del *stent*?

David Antoniucci[1], Alfredo E. Rodríguez[2]

ABSTRACT

Duration of dual antiplatelet therapy after drug eluting stent implantation is not well stablished in spite of several randomized studies.
In this article authors analyzed and described results from these trials.

Keywords: *DAPT, drug-eluting stents, stents thrombosis, bleeding, stents.*

RESUMEN

En años recientes, varios estudios aleatorizados han tratado de responder la pregunta de hasta cuánto tiempo después del implante de un *stent* farmacologico es necesario continuar con la doble terapéutica antiplaquetaria.
En esta revisión los autores describen y analizan los resultados de esos estudios.

Palabras claves: *DAPT, stents liberadores de drogas, trombosis del stent, sangrado, stents.*

Revista Argentina de Cardioangiología Intervencionista 2015;6(3):126-128

In recent years several randomized clinical trials (RCT) sought to determine the optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary interventions (PCI) with drug-eluting stent (DES) implantation, since a mayor safety concern with 1st generation DES was late and very late stent thrombosis[1,2]. The introduction of the 2nd second and 3rd generation DES was associated with a lower risk of stent thrombosis rendering questionable long-term DAPT after DES implantation[3,4].
As expected the use of long-term DAPT is associated with greater incidence of bleeding that may be particularly high in some sub-groups of patients such as elderly, recent surgery, anticoagulant treatment, frialty and others.
We identified 10 RCTs[5-14]conducted in the last 5 years in order to respond to the question of how long after DES implantation our patients should take DAPT **(Table 1)**.
Designs of these studies are not uniform with have differences in clinical patient characteristics, stent type, time of randomization after PCI, follow-up duration, definition of major and minor bleedings, and also which type P2Y12 inhibitor used.
The first eight studies in general were in favor of a short-term DAPT, although the short period was defined among 3, 6 and 12 months after PCI with stent deployment, while long-term DAPT was defined as 12, 24, 30 and 36 months after stent deployment.
The main results of these RCTs both short-term or long-term DAPT post DES implantation had similar rates of major adverse ischemic events including stent thrombosis while long-term DAPT was linked with a significantly higher incidence of bleeding complications at follow up.
We have to take in account that all these studies included low-risk patients, while patients at high risk of stent thrombosis were excluded from randomization (multiple stents, severe left ventricular dysfunction, renal insufficiency, etc.). Again, another major limitation of some study is the type of stent used. As example, in the OPTIMIZE RCT, was used a zotarolimus-eluting stent with a platform associated with a very high late loss (0.62 mm) similar or even higher than bare-metal stents [15,16]. As a consequence conclusion from this trial, that was associated with a very low thrombosis rate, should be considered with caution and expanded to other DES types with lower late loss and lower restenosis rate at follow-up.

1. Cardiology Division, Careggi Hospital, Florence, Italy.
2. Cardiac Unit, Sanatorio Otamendi, Buenos Aires, Argentina.

✉ Correspondence: *david.antoniucci@virgilio.it*

The authors declare no conflicts of interest

Received: 19/08/2015 | Accepted: 25/08/2015

Table 1. Dual antiplatelet therapy trials. Landmark randomized clinical trials.

	Patient´s number	*DAPT duration*	*DES type*	*Primary endpoint*
RESET[5]	2148	12 vs 24 months	ZES, SES, EES	Cardiac death, MI, TVR, stent thrombosis or bleeding
ITALIC[6]	1953	6 to 24 months	EES	Overall death, MI, CVA, TVR or major bleeding.
ARCTIC-INTERRUPTION[7]	2440	12 vs 24 months	All DES	Overall death, MI, CVA or urgent revascularization.
REAL-LATE[8])	2000	12 vs 24 months	All DES	Cardiac death or MI
ZEST-LATE[8]	2000	12 vs 24 months	SES, PES, ZES	Cardiac death or MI
PRODIGY[9]	1870	12 vs 24 months	EES, PES, ZES, BMS	Overall death, MI or CVA
EXCELLENT[10]	1443	6 vs 12 months	SES, ZES	TVF (cardiac death, MI, ischemic-driven target vessel revascularization)
OPTIMIZE[11]	3120	3 vs 12 months	ZES	Overall death, MI, CVA or major bleeding.
ISAR-SAFE[12]	6000	6 vs 12 months	All DES	Overall death, MI, CVA, TIMI major bleeding
PEGASUS-TIMI 53[13]	21162	33 months (mean)	All DES	Cardiovascular death, MI or CVA.
DAPT[14]	20645	12 vs 30 months	All DES, BMS	-Overall death, MI or CVA -Definitive/Probable stent thrombosis

DAPT: dual antiplatelet therapy. DES: drug eluting stent. ZES: zotarolimus eluting stent. SES: sirolimus eluting stent. EES: everolimus eluting stent. MI; myocardial infarction. TVR: target vessel revascularization. CVA: cerebrovascular accident. PES: paclitaxel eluting stent. BMS: bare metal stent. TVF: target vessel failure. TIMI: thrombolysis in myocardial infarction.

If we take all these trials without criticism and the limitations described above, we can made a wrong conclusion from the first 8 RCT and assume that 3 to 6 months DAPT post DES implantation would be enough to prevent either stent thrombosis and/or bleeding complications.

The last two trials included were the DAPT and PEGASUS trials, and both are in favor of long-term use of thienopyridine plus aspirin after stent implantation. The DAPT collected the largest number of patients after PCI and stent implantation although less than 50% of the initial population was randomized at 12 months after PCI.

Major findings of this study were that patients taking DAPT at 30 months had lower risk of stent thrombosis, myocardial infarction (MI) and major ischemic adverse events compared to those who stopped DAPT at 12 months, while patients with long-term DAPT had an increased risk of moderate or severe bleeding. Limitations of this study were time of randomization and stents types (were included BMS and 1st generation DES not more available.

The last study in table, PEGASUS trial differently from the others studies enrolled exclusively patients with acute coronary syndromes (STEMI and NSTEMI). Major findings of this study were that 3 years of DAPT (ticagrelor plus aspirin) after DES implantation was associated with significant less incidence of cardiac death, MI and stroke and a higher incidence of bleeding. However, fatal bleedings, or intracranial hemorrhage or hemorrhagic stroke was not significantly different in the 2 study arms.

Finally and in agreement with DAPT trial [14], recently was presented at European Congress in London results from OPTIDUAL trial which a post hoc analysis showed there was a strong trend toward fewer ischemic events in the long-term group, death/MI/stoke/major bleed were 4.2% and 6.4% with 4 and 1 year of DAPT respectively p=0.06, and no sign of an increased major bleeding risk [17] If we have to formulate a final statement from all findings summarized here, we should not be able to give a definite answer to the question of how long our patients should be treated with DAPT, and probably we should be able to tailor the treatment duration according to a realistic balance of the risk of stent thrombosis with the risk of bleeding.

It is easy to predict that last generation DES with biodegradable polymers, thinner stent struts, abluminal coating allowing less amount of immunosuppressive drug, which translate to a faster covering of stent struts (4 weeks after implantation) will allow short-term DAPT safe in terms of stent thrombosis in the majority patients [18-20].

REFERENCES

1. *Rodriguez AE, Rodriguez-Granillo GA, Palacios IF. Late stent thrombosis: the Damocle's sword of drug eluting stents? EuroIntervention 2007 Feb;2(4):512-7.*
2. *Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005 Jun 21;45(12):2088-92.*
3. *Serruys PW, Farooq V, Kalesan B et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. JACC Cardiovasc Interv 2013 Aug;6(8):777-89.*
4. *Kereiakes DJ, Smits PC, Kedhi E, et al. Predictors of death or myocardial infarction, ischaemic-driven revascularisation, and major adverse cardiovascular events following everolimus-eluting or paclitaxel-eluting stent deployment: pooled analysis from the SPIRIT II, III, IV and COMPARE trials. EuroIntervention 2011 May;7(1):74-83.*
5. *Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol 2012 Oct 9;60(15):1340-8.*
6. *Gilard M, Barragan P, Noryani AA, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. J Am Coll Cardiol 2015 Mar 3;65(8):777-86.*

7. *Montalescot G, Rangé G, Silvain J, et al. High on-treatment platelet reactivity as a risk factor for secondary prevention after coronary stent revascularization: A landmark analysis of the ARCTIC study. Circulation 2014 May 27;129(21):2136-43.*
8. *Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med 2010 Apr 15;362(15):1374-82.*
9. *Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012 Apr 24;125(16):2015-26.*
10. *Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation 2012 Jan 24;125(3):505-13.*
11. *Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA 2013 Dec 18;310(23):2510-22.*
12. *Schulz-Schüpke S, Byrne RA, Ten Berg JM, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J 2015 May 21;36(20):1252-63.*
13. *Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015 May 7;372(19):1791-800.*
14. *Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014 Dec 4;371(23):2155-66.*
15. *Feres F, Andrade PB, Costa RA, et al. Angiographic and intravascular ultrasound findings following implantation of the Endeavor zotarolimus-eluting stents in patients from the real-world clinical practice. EuroIntervention 2009 Aug;5(3):355-62.*
16. *Cassese S, De Luca G, Ribichini F, et al. ORAI iMmunosuppressive therapy to prevent in-Stent rEstenosiS (RAMSES) cooperation: a patient-level meta-analysis of randomized trials. Atherosclerosis 2014 Dec;237(2):410-417.*
17. *OPTIDUAL: More Debate on Length of Dual Antiplatelet Therapy Post-DES; Heartwire from Medscape, 2015-08-31.*
18. *Gao Z, Zhang R, Xu B, et al Safety and efficacy of a novel abluminal groove-filled biodegradable polymer sirolimus-eluting stent for the treatment of de novo coronary lesions: two-year results from a prospective patient-level pooled analysis of TARGET trials. Catheter Cardiovasc Interv 2015 Mar;85 Suppl 1:734-43. doi: 10.1002/ccd.25861. Epub 2015 Feb 19.*
19. *Otsuka F, Cheng Q, Yahagi K et al. Acute Thrombogenicity of a Durable Polymer Everolimus-Eluting Stent Relative to Contemporary Drug-Eluting Stents With Biodegradable Polymer Coatings Assessed Ex Vivo in a Swine Shunt Model. JACC Cardiovasc Interv 2015 Aug 17;8(9):1248-60. doi: 10.1016/j.jcin.2015.03.029.*
20. *Mauro D, Cherro A, Rubilar B, et al. Recomendaciones para la optimización de la terapia de antiagregación dual en la angioplastia coronaria con stent. Consensos y normas del Colegio Argentino de Cardioangiólogos Intervencionistas – CACI; Revista Argentina de Cardioangiologia Intervencionista 2015;6(1):0020 -0026.*