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?

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ABSTRACT
Duration of dual antiplatelet therapy after drug eluting stent implantation is not well established 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 farmacológico 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.

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 major safety concern with 1st generation DES was late and very late stent thrombosis¹,². 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 implantation³,⁴. 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, friaity and others.

We identified 10 RCTs⁵-¹⁴ 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 stents¹⁵,¹⁶. 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.
If we take all these trials without criticism and the limitations described above, we can make 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).

The study in table, PEGASUS trial differently from the others studies enrolled exclusively patients with acute coronary syndromes (STEMI and NSTE-MI). 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, 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. 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.

REFERENCES


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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient’s number</th>
<th>DAPT duration</th>
<th>DES type</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESET1</td>
<td>2148</td>
<td>12 vs 24 months</td>
<td>ZES, SES, EES</td>
<td>Cardiac death, MI, TVR, stent thrombosis or bleeding</td>
</tr>
<tr>
<td>ITALIC2</td>
<td>1953</td>
<td>6 to 24 months</td>
<td>EES</td>
<td>Overall death, MI, CVA, TVR or major bleeding.</td>
</tr>
<tr>
<td>ARCTIC-INTERUPTION3</td>
<td>2440</td>
<td>12 vs 24 months</td>
<td>All DES</td>
<td>Overall death, MI, CVA or urgent revascularization.</td>
</tr>
<tr>
<td>REAL-LATE4</td>
<td>2000</td>
<td>12 vs 24 months</td>
<td>All DES</td>
<td>Cardiac death or MI</td>
</tr>
<tr>
<td>ZEST-LATE4</td>
<td>2000</td>
<td>12 vs 24 months</td>
<td>SES, PES, ZES</td>
<td>Cardiac death or MI</td>
</tr>
<tr>
<td>PRODIGY5</td>
<td>1870</td>
<td>12 vs 24 months</td>
<td>EES, PES, ZES, BMS</td>
<td>Overall death, MI or CVA</td>
</tr>
<tr>
<td>EXCELLENT6</td>
<td>1443</td>
<td>6 vs 12 months</td>
<td>SES, ZES</td>
<td>TFV (cardiac death, MI, ischemic-driven target vessel revascularization)</td>
</tr>
<tr>
<td>OPTIMIZE7</td>
<td>3120</td>
<td>3 vs 12 months</td>
<td>ZES</td>
<td>Overall death, MI, CVA or major bleeding.</td>
</tr>
<tr>
<td>ISAR-SAFE8</td>
<td>6000</td>
<td>6 vs 12 months</td>
<td>All DES</td>
<td>Overall death, MI, CVA, TIMI major bleeding.</td>
</tr>
<tr>
<td>PEGASUS-TIMI 539</td>
<td>21162</td>
<td>33 months (mean)</td>
<td>All DES</td>
<td>Cardiovascular death, MI or CVA.</td>
</tr>
<tr>
<td>DAPT10</td>
<td>20645</td>
<td>12 vs 30 months</td>
<td>All DES, BMS</td>
<td>Overall death, MI or CVA</td>
</tr>
</tbody>
</table>


