Expert Overview: How long to Continue DAPT After Elective Stenting

Dual antiplatelet therapy is among the most intensively investigated treatment options in the field of cardiovascular medicine. The original need to investigate longer DAPT regimens arose from concerns regarding late and very

late stent thrombosis associated with first-generation DES.

The advent of safer newer-generation DES and the results of the most recent randomized controlled trials (RCTs) have led to a major shift in the way DAPT is considered and used in clinical practice. The risks of late and very late stent thrombosis have declined considerably with the advent of the

newer-generation DES. The risk for bleeding associated with prolongation of DAPT no longer seems to be justified by the small absolute benefit observed in terms of preventing very late stent thrombosis.

Even back in 2015, Robert Byrne and colleagues were reporting the good news/bad news results of a large meta-analysis evaluating 10 RCTs totaling

32,194 participants.**(Ref.1)** Prolonging the duration of DAPT after DES implantation worked in that it reduced the risk of stent thrombosis and myocardial infarction, but these benefits came at a steep cost: an increased risk of major bleeding and death.

Now investigations are concerned with how short the duration of DAPT can be and still optimize the reduction of

ischemic risk while limiting bleeding. The GLOBAL LEADERS evaluated 1 month of DAPT, while the SMART CHOICE, STOPDAPT-2, and TWILIGHT trials evaluated 3 months of DAPT. After those periods, the aspirin was stopped and patients continued with P2Y12 inhibitor monotherapy. In short, this approach led to less bleeding with no

cost in terms of excess ischemic events than continuing on with DAPT.

The problem with so much data is that it has created confusion about the optimal type and duration of DAPT. Recently, a team of investigators in China conducted a systematic review and network meta-analysis of 17 studies (n = 46,864).**(Ref.2)** All the RCTs had compared two of three DAPT durations:

short term (≤6 months), standard term (12 months), and long term (>12 months) after PCI with DES.The primary study outcomes were cardiac or noncardiac death, all-cause mortality, myocardial infarction, stent thrombosis, and all bleeding events. Long-term DAPT resulted in higher rates of major bleeding and noncardiac death (**Table**); standard-term DAPT was

associated with similar ischemic outcomes but higher rates of any bleeding (**Table**).No noticeable difference was observed in other primary endpoints. In subgroup analysis, long-term DAPT led to higher all-cause mortality than short-term DAPT in patients receiving newer-generation DES (odds ratio: 1.99; 95% confidence interval: 1.04 to 3.81).

Network Meta-analysis: Comparison of Endpoints with 3 Durations of DAPT

	Odds Ratio (95% CI)	
	Long-term vs. Short-term	**Standard-term vs. Short-term**
All-cause mortality	1.18 (0.93-1.49)	1.08 (0.82-1.43)
Cardiac death	1.28 (0.88-1.86)	1.12 (0.80-1.58)
Noncardiac death	1.63 (1.03-2.59)	1.09 (0.67-1.77)
Major bleeding	1.78 (1.27-2.49)	1.28 (0.91-1.80)
Any bleeding	2.13 (1.46-3.10)	1.39 (1.01-1.92)
Myocardial infarction	0.63 (0.46-0.86)	0.92 (0.70-1.21)
Definite/probable ST	0.57 (0.34-0.95)	0.98 (0.59-1.64)
Stroke	1.08 (0.77-1.51)	1.04 (0.74-1.47)
Net adverse clinical events	0.88 (0.67-1.15)	0.91 (0.77-1.08)

It should be noted that short-term DAPT even presented similar efficacy and safety to standard-term DAPT in patients presenting with acute coronary syndrome treated with newer-generation DES. The authors noted the heterogeneity of pooled trials was low, providing confidence in the interpretation of the results.

Overall, the authors of the new meta-analysis concluded that short-term DAPT (with clopidogrel) could be considered for most patients after PCI with DES. Long-term DAPT resulted in more death and bleeding-related events, while standard-term DAPT presented similar efficacy and safety.

Guidelines

The most recent guidelines come from Europe and were coauthored by Dr. Byrne.**(Ref.3)**

For patients with stable CAD treated with PCI, the guidelines committee wrote, prior recommendations of 12 months or more of DAPT were "arbitrary" and "based on expert

opinions after first-generation DES, irrespective of clinical presentation."

Consequently, the updated European guidelines state that for patients with stable CAD being treated with PCI, *irrespective of the type of metallic stent implanted*, the duration of DAPT is 6 months, and based upon the presence of very high or high life-threatening risk of bleeding the DAPT duration will be

shortened to 1 and 3 months respectively. **(Ref:5)**

In a cohort of patients with CCS in whom DAPT can not be used because of aspirin intolerance, Prasugrel or Ticagrelor may be considered (Class 2b) at least as intitial therapy, as antiplatelet monotherapy in high thrombotic risk situations such as

complex LM, MV stenting and so forth. (**Ref:5)**

For patients in whom the ischemic risk prevails over the risk of bleeding, a longer duration may be considered.

In patients with CCS and in sinus rhythm adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered (class

2a) in patients with high risk of ischemic events and without high bleeding risk. The same statement but with class 2b, may be considered in CCS patients with in at least moderate risk of ischemic events and without high bleeding risk. Among the recommended add-on second drugs is Rivaroxaban 2.5 Mg b.i.d (**Ref:5)**

The updated guidelines also note that the need for a short regimen of DAPT should no longer justify the use of bare-metal stents instead of newer-generation DES. Earlier guidelines had established a 1-month course of DAPT as appropriate after placement of a bare-metal stent, but it was noted that this recommendation was never supported

by evidence that was particularly strong.

What about patients with an indication for oral anticoagulation (OAC)? Compared with OAC alone, the guidelines state that the addition of DAPT to OAC therapy results in at least a two- to three-fold increase in bleeding

complications. These patients should be considered at high risk for bleeding.

The default strategy is continuation of triple therapy for < 1 week, and with discontinuation of ASA, OAC and antiplatelet monontherapy continued for the suggested period of time.

If triple therapy is deemed necessary, in *very high ischemic risk patients* most experts would probably agree to limit it

to no more than 6 months – and that still involves considerable bleeding risk. There is some evidence that 1 month of triple therapy may be enough, but as for what is best between 1 and 6 months, it should be Tailored on the basis of severity of Ischemic risk, such as LM stenting, complex bifurcation, CTO, overlapping stenting with> 60 mm length, and so forth. (**Ref:5)**

Having said that, as for the duration of triple therapy, the updated European guidelines state it should be limited to a maximum of 6 months or simply changed to dual anti-thrombotic therapy after hospital discharge as the default strategy.

As pointed out Clinicians need to consider factors that influence ischemic risk (e.g., complexity of treated CAD,

amount of disease left untreated, technical considerations regarding stent implantation techniques, and results) as well as bleeding risk.

The most recent network meta-analysis suggests that, in comparison with 12-month DAPT, short-term DAPT followed by P2Y12 inhibitor monotherapy reduces major bleeding after percutaneous coronary intervention

with drug-eluting stents, whereas extended-term DAPT reduces myocardial infarction at the expense of more bleeding events.**(Ref. 4)**

Take-home Messages:

- For patients with stable coronary artery disease (CAD) who are undergoing percutaneous coronary intervention (PCI) and placement of

a drug-eluting stent (DES), the standard recommended duration of dual antiplatelet therapy (DAPT) is 6 months; however, that may not be the optimal duration.

- The most recent data come from a large meta-analysis of randomized trials. Regardless of clinical presentation, short-term DAPT (clopidogrel; <6 months) showed

the best balance of benefit to risk. Long-term DAPT (>12 months) led to higher rates of major bleeding and noncardiac death, while standard-term DAPT was associated with similar efficacy to short-term DAPT but more bleeding.

- Although clinicians determining the optimal duration of DAPT for an individual patient should consider

personal risks for ischemia and bleeding, the data suggest short-term DAPT could be considered for most patients after PCI with newer-generation DES.

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