S Silber

# The RESOLUTE clinical programme: one month DAPT data presented at TCT

Preliminary analysis of pooled data from four of the RESOLUTE clinical trials has recently suggested that patients who discontinued dual antiplatelet therapy four weeks after stent implantation may not be at increased risk of stent thrombosis compared with those who maintained therapy for one year post-intervention. We caught up with Professor Sigmund Silber from Munich, who presented these data at the recent TCT 2012 meeting in Miami, to find out more.

## What was the rationale for this analysis of the pooled RESOLUTE data?

We have known for many years that prolonged dual antiplatelet therapy (DAPT) is very important to prevent stent thrombosis (ST) after the implantation of bare or drug-eluting stents (DES). However, there is some discrepancy in the guidelines regarding the minimum duration of DAPT after implantation of DES in stable coronary patients. According to the European guidelines published in 2005[1] and the update published in 2010,[2] patients should be prescribed DAPT for at least six months, while in the American guidelines[3] it is at least one year. At first glance, it may not be obvious why there is such a difference between Europe and the United States. The most likely explanation is that, to date, no prospective randomized trial has ever evaluated the efficacy and safety of six months versus 12 months of DAPT. Therefore, the guideline recommendations are based on observational studies and individual experience.

For first-generation DES, we know that if you discontinue DAPT within the first six months, there is a considerably increased risk of ST, which is dangerous for the patient, because ST leads to myocardial infarction (MI) in almost every second patient, and may therefore result in death.

With the newer generation DES, we do not have data from randomized trials that have investigated the appropriate duration of dual antiplatelet therapy. We do, however, have a considerable volume of data from clinical trials investigating the safety and efficacy of the newer DES. We took the opportunity to carry out a *post hoc* analysis of data from four of the studies that were part of the RESOLUTE clinical trial programme for the zotarolimus-eluting Resolute stent (Medtronic, Inc.). We looked at rates of ST in relation to DAPT interruption or discontinuation. It is, of course, important to keep in mind that these data did not come from randomized clinical trials regarding the duration of DAPT.

## Can you tell us a little more about the analysis?

We analyzed data from the following four studies: the randomized RESOLUTE All-Comers study (n=2,292), with a follow-up of three years; the RESOLUTE International study (n=2,349) an observational study with a follow-up of three years; the RESOLUTE US registry (n=1,402) with a follow-up of two years; and finally, the RESOLUTE Japan trial (n=100), in which patient follow-up was for two years.

Of these patients, 907 had discontinued or interrupted the DAPT from one month after stent implantation; about two-thirds of these patients had totally discontinued and about one-third had interrupted and then re-started DAPT at a later point in time.

When we looked at the analysis of discontinuation of DAPT from one month to one year, not a single instance of ST occurred in the follow-up period. This means that if from an analysis perspective the patient was off DAPT, having had at least four weeks of DAPT, there was no increased risk of ST in this subgroup analysis; however, if the patient discontinued before the

first four weeks after stent implantation, there was a stent thrombosis rate of about 3%. This is a very striking result.

I do not mean to suggest that we should recommend one month of DAPT for patients after Resolute stent implantation, but this data is reassuring that if they interrupt or discontinue there is a very low risk of ST. We will see if this data, on further analysis, supports the idea that discontinuation for cause like urgent surgery, is associated with a low ST rate. We do not yet have the data analysis to support discontinuation in the high-risk population.

This is a *post hoc* analysis and, of course, there are limitations to such data. Furthermore, I think it is very important to make clear that this is not the final analysis; it is only a preliminary analysis. There is still a considerable amount of further evaluation to do to confirm these findings.

## Do you think the RESOLUTE data are representative of the patients seen in general clinical practice?

Yes. The four studies included in the pooled analysis were not restricted to a specific population and so could more or less be described as quasi all-comers studies. We will need to examine the data further to determine the profile of the patients who discontinued DAPT at one month and a key question to which we do not yet know the answer is why DAPT was discontinued in these patients.

Interestingly, in the analyses carried out to date with the Resolute stent in over 5,000 patients, the risk of ST was the same in patients with non-insulin treated diabetes as in non-diabetic patients. That is to say, diabetes did not actually appear to be a risk factor for clinical outcome any more.

## Can you help to explain to us why these findings might be beneficial in clinical practice?

Because of bleeding: DAPT increases the risk of bleeding compared with single antiplatelet therapy, so the combination of aspirin plus clopidogrel, prasugrel or ticagrelor increases bleeding. Each of these drugs increases bleeding and so when you combine those drugs you get more bleeding and bleeding negatively affects even long-term prognosis. Ideally, we would minimize bleeding by cutting back the duration of DAPT.

Another benefit is adherence to DAPT prescription. Sometimes we prefer to implant a bare metal stent (BMS) because the patient will be unable or unwilling to comply with the DAPT regimen, for example an elderly patient who may already take a large number of tablets. However, if the data show a reduced risk after only four weeks of DAPT, DES may become an option in such patients too. Indeed, data from the XIMA study (also presented at TCT 2012), which investigated implantation of BMS versus DES in elderly (>80 years old) patients, observed that DES worked very well in those patients but there is an increased bleeding rate over time. A DES requiring only four weeks of DAPT would offer a particular advantage for elderly patients.

Furthermore, as life expectancy increases and our society becomes older, the incidence of atrial fibrillation (AF), a very age-dependent disease, increases. We will, therefore, see many more patients with AF, which must be managed with anticoagulation. This means treatment with vitamin K antagonists or new drugs such as rivaroxaban, dabigatran or apixiban, which help to prevent stroke and cerebral bleeding. Since "triple therapy" (DAPT + anticoagulation) further increases the risk of bleeding in patients with AF it would be better to minimize the duration of DAPT for a DES than to use a BMS.

## How compatible were the data across the four RESOLUTE studies?

The nice fact about the RESOLUTE programme is that the protocols were harmonized before the studies started so the definitions were the same in all of the studies. This means that the data are really compatible. All the events in the four studies included in our pooled analysis were adjudicated by an independent data and safety monitoring committee. Such activities help to ensure the quality of the dataset.

## What further data would be beneficial to support this story?

Randomized controlled trials represent the gold standard for evidence-based medicine. Therefore a randomized trial of four weeks versus six months of DAPT would be very important. At present, there are a number of ongoing randomized trials comparing different durations of dual antiplatelet

therapy, such as one year of DAPT vs more than one year of DAPT or 6 months vs 12 months. However, such studies do not solve the need for studies investigating shorter treatment durations.

Without results from a randomized clinical trial of four weeks versus six months DAPT, I would continue to use the European Society recommendations of at least six months.

However, if for some reason a patient has to discontinue DAPT before 6 months, I think these new data can help us to feel more confident in doing so after implantation of newer generation DES.

**Address for correspondence**
Professor Dr. med. Sigmund Silber
FESC, FACC, FAHA
Heart Center at the Isar
Academic teaching site of the
University of Munich
Am Isarkanal 36
81379 Munich
Germany

t: ++49-89-74215130
f: ++49-89-74215131

sigmund@silber.com
www.sigmund-silber.com

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