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DAPT and DES in coronary artery disease: Is it time to revisit the guidelines?

Interventional cardiologists Sigmund Silber (Cardiology Practice and Heart Center at the Isar Munich, Germany), Azeem Latib (EMO-GVM Centro Cuore Columbus and San Raffaele Scientific Institute, Milan, Italy) and Alexandre Abizaid (Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil) discussed, at a roundtable organised by *Cardiovascular News* with and unrestricted educational grant from Medtronic, whether the current US and European guidelines on the duration of dual antiplatelet therapy (DAPT) for patients with stable coronary artery disease treated with drug-eluting stents (DES) should be revisited. Abizaid first introduced the subject with a review of the current guidelines followed by a discussion moderated by Flavio Ribichini (Cardiovascular Interventional Unit, University of Verona, Verona, Italy)

Past and current guidelines review

In the first part of the roundtable, Abizaid presented an overview of the early and current indications of DAPT coronary artery disease patients who are treated with DES.

"In the early years of DES (2002–2004) the recommendation was three months of DAPT for sirolimus-eluting stents and six months for paclitaxel-eluting stents," said Abizaid.

Later, in 2006, the results from the SCAAR registry raised some concerns in terms of late stent thrombosis showing that mortality would be higher with DES vs. bare metal stents. He said that these data along with a recommendation, in 2007, from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons and American Dental Association, based on the Duke Database, "provoked" the FDA to recommended 12-month DAPT after the placement of a drug-eluting stent. Abizaid highlighted that this decision was made based on retrospective data and during that time "there was no randomised data to prove that this was the best indication," he said.

Abizaid also referred to data from the Bern-Rotterdam registry, published in *The Lancet*, by Daemen J, Serruys P *et al*, which showed a 0.6% stent thrombosis rate every year, during three years, after DES (first generation Cypher/Cordis and Taxus/Boston Scientific) implantation. Another paper, published in *Circulation* in 2007 by Airoldi F, Colombo A, found that most of the stent thrombosis events would occur in the first six months. These data "raised further discussion," noted Abizaid. More recently, latest US (*Circulation* 2011, Levine GN) and European (*European Heart Journal* 2010, Wijns W) guidelines recommended at least 12-month DAPT if patients are not at high risk of bleeding (class I, evidence B) in the USA and six to 12-month DAPT for patients receiving DES with stable angina and one year for patients with unstable angina in Europe.

From left to right: Sigmund Silber, Azeem Latib, Alexandre Abizaid and Flavio Ribichini

Discussion

Ribichini (R): The latest guidelines on duration of DAPT after implantation of a DES in patients who undergo percutaneous coronary artery intervention came out in Europe in 2010 and in the USA in 2011. They recommended six months and one year, respectively. Do you think it was an appropriate indication?

Abizaid (A): During that time, most data were generated with first generation drug-eluting stents. I think it was appropriate at that time; however, we could discuss if this was applicable for all kinds of patients and anatomies.

Latib (L): I agree. It was a fair statement based on patient's safety; however, it was not supported by a lot of data, just two non-randomised registries [SCAAR and Bern-Rotterdam]. It is worthwhile to highlight how the European and the American guidelines diverted, with the American guidelines recommending a minimum of 12 months and the European guidelines saying that six months of DAPT might be ok in a lot of patients. At that time, it was applicable to the first generation drug-eluting stents, which means that it may not apply today to the second generation devices.

Silber (S): The very first European guidelines came out in 2005. At that time, there was not a single randomised, controlled trial with different DAPT duration so we decided, based on observational data, to recommend at least six months. But one year later, the "Barcelona firestorm"* came up and the Americans became a little bit nervous and jumped immediately from six months to one year DAPT, although

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*Barcelona firestorm: At the European Society of Cardiology congress 2006 two independent meta-analyses by Alain Nordmann, Basel, Switzerland, and Edoardo Camezino, Geneva, Switzerland, raised the possibility that first generation DES might increase the risk of death due to an increased incidence of late-stent thrombosis.

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there were absolutely no data to justify the at least one-year recommendation. Today, eight years after the first recommendation of the European Society of Cardiology (ESC) guidelines, we still do not have data to change the recommendation from six to 12 months.

Moderator's comment: This recommendation was based on the large number of patients with acute coronary syndrome undergoing PCI with DES. Although it is true that the recommendation was not specific for DES but the acute coronary syndrome itself.

Alexandre Abizaid

R: Apart from the clinical indications (eg. acute coronary syndrome, diabetes), there are lesion characteristics that condition the kind of angioplasty we perform in long lesions, left main disease or bifurcations. This would potentially let us recommend more caution and therefore longer DAPT. What are your thoughts?

A: I think you are right, but this is more based on personal experience. If I have a diabetic patient with left main disease, bifurcation, and perhaps a chronic total occlusion in the right coronary artery with multiple DES, naturally I will go for one year or sometimes even more. But again, where is the randomised trial to prove the real benefit of giving prolonged DAPT in this patient subset?

S: Guidelines are not the law, they are just recommendations and in every guideline it is written that the patient comes first and you have to make individual decisions. In complex lesions, bifurcations, etc, of course we tend to go for longer DAPT duration but we still do not have the data to support this. We know diabetic patients have more complications, but with newer generation drug-eluting stents there are data showing that these patients are not at a higher risk than non-diabetic patients (unless they are insulin dependent). But if the patients are not insulin dependent, I think the challenge of treating a diabetic patient is much better managed today than it was five years ago.

R: In terms of safety, what is more important, the stent or the technique of implantation?

S: Both are important. We should always have in mind that a drug-eluting stent is not a car. If a car has a problem there are recalls; if a heart valve has a problem you can also "recall" it. The stent is forever with the patient, so the decision of what drug-eluting stent to use is decisive and we should be very careful on making this decision. We need to know the data. There are some drug-eluting stents on the market with hardly any data. We should ask ourselves before we implant a drug-eluting stent, "Would I—as the cardiologist—like to have this drug-eluting stent forever in my body?" If I say yes, then we should implant it in the patient.

L: I think you cannot separate the stent from the technique of implantation. If you are going to use a drug-eluting stent just because it is the best on the market, with the best data, it does not mean that you can be sloppy on how you will put it into patients. I think technique goes with choice of device, and you have to make sure you are implanting stents properly. To reiterate what Silber says, there are a lot of new stents in the market in Europe with very little data to support them. If we are talking about using second generation drug-eluting stents we should see what data are available to support them.

One-month and three-month DAPT, is it feasible?

In the second part of the roundtable, Latib presented data demonstrating that DAPT longer than 12 months increases the risk of bleeding; he also talked about differences between first and second generation DES and their impact on DAPT duration. Silber spoke about the results of the RESOLUTE clinical programme. After these presentations, the physicians discussed the benefits and challenges of prescribing DAPT for 12, six, three and less than three months. They also talked about the differences between discontinuation and interruption of DAPT, in specific cases, with second generation DES and the role of bioabsorbable scaffolds to determine DAPT duration

DAPT longer than 12 months increases risk of bleeding

Latib presented clinical evidence showing that DAPT longer than 12 months increases the risk of bleeding. He said that the first study assessing this issue was the combined data from the REAL-LATE and ZEST-LATE studies, published in the *New England Journal of Medicine*. This study randomised 2,701 patients that were free from events at 12 months to either stopping clopidogrel or continuing DAPT until two years after DES implantation. At two years, Latib said, there was no difference in the primary endpoint of cardiac death or myocardial infarction, and no difference in the secondary endpoints of target lesion revascularisation and stent thrombosis. "While there appeared to be no advantage from continuing DAPT for two years, there was a trend that the risk of thrombolysis in myocardial infarction (TIMI) major bleeding might be higher," he commented.

Azeem Latib

Another relevant study in this area, according to Latib, was the PRODIGY study, which was specifically designed to compare 24-month DAPT to six-month DAPT duration. Patients were randomised in a 1:1:1:1 fashion to Xience V (Abbott), Taxus (Boston Scientific), Endeavor (Medtronic) or a bare metal stent. The study results showed no difference in the primary endpoint (overall death, myocardial infarction or cerebrovascular accident) in the group treated with a short DAPT duration versus a prolonged course of DAPT. However, "the risk of bleeding and requirement for blood transfusion were significantly higher with prolonged DAPT duration," he highlighted. A further analysis of the risk of bleeding demonstrated that there was a continuous risk of bleeding (0.2%/month or 3.8%/year) in patients who continued DAPT for 24 months, Latib added.

Latib also addressed the question whether six-month DAPT may be sufficient and whether the duration of DAPT should depend on the type of DES implanted (either first generation or second generation DES). The EXCELLENT trial, Latib said, attempted to address this question by randomising patients to six vs. 12 months of DAPT and then to a second generation everolimus-eluting stent (EES) or a first generation

sirolimus-eluting stent (SES). At 12 months, there was no difference in the primary endpoint of target vessel failure or in the safety endpoint of death, myocardial infarction, stent thrombosis, cerebrovascular accident, or TIMI major bleeding between the groups randomised to six vs. 12 months of DAPT. However, Latib said, when the data were analysed by stent type, there was no difference in target vessel failure for EES for six vs. 12 months; whereas in the SES group, patients in the six-month DAPT group had almost twice as many events as the group who took the conventional DAPT duration of 12 months. A sub-analysis of the PRODIGY study also suggested that not all DES are equal, particularly with regards to the duration of DAPT required. "These studies suggest that for first generation DES, 12-month DAPT is still needed and six-month DAPT may be sufficient for the second generation DES," he said.

RESOLUTE clinical programme shows low stent thrombosis after one-month of interrupted DAPT

It is unclear if earlier interruption and/or discontinuation of DAPT is associated with a higher risk of stent thrombosis, particularly with newer generation DES, noted Silber in his presentation at the roundtable. "In daily practice, we are often confronted with the necessity of a premature (before the six-month recommendation from the European guidelines) interruption of DAPT for unplanned circumstances, especially surgical procedures," he said. An analysis of the RESOLUTE clinical programme by Windecker S, Silber S *et al* [submitted] helped to answer this question, Silber commented.

The RESOLUTE clinical programme integrated eight clinical studies with the Resolute zotarolimus-eluting stent (Medtronic) in over 5,000 patients. Within the first month, after stent implantation, 126 patients interrupted DAPT for more than two weeks. After the first month, following stent implantation up to one year, 783 patients interrupted DAPT for at least two weeks. The analysis showed, according to Silber, that within one year, after stent implantation, definite or probable stent thrombosis occurred in 5.2% of the patients who interrupted within the first month, whereas there was no stent thrombosis in the patients interrupting DAPT after the first month. The results from the one-year data of the global RESOLUTE clinical programme "indicate low stent thrombosis rates for those who interrupted or discontinued DAPT after one month for unplanned reasons. Nevertheless, physicians should still follow the current ESC percutaneous coronary intervention guidelines which recommend the minimum duration of DAPT for six months, but the present analysis may provide reassurance for clinicians and patients implanted with the Resolute DES who may need to interrupt or discontinue the medication before the recommended DAPT duration for unplanned reasons," said Silber.

He also highlighted some other randomised controlled trials that are currently evaluating varied DAPT regimens such as: the DAPT trial (12 months vs. 30 months), ISAR-SAFE (six months vs. 12 months), OPTIMIZE (three months vs. 12 months), ITALIC (six months vs. 12 months) and SECURITY (six months vs. 12 months) [ongoing studies].

Moderator's comment: Although we do not recommend DAPT interruption after 30 days, this is certainly safer now, with Xience or Resolute, than it was with first generation DES in the case of absolute need for premature DAPT interruption—for example for urgent unplanned surgery of major bleeding.

Active RCTs evaluating varied DAPT regimens

Trial name	Inclusion group, n	DAPT duration	DES type	Primary endpoint	Key secondary endpoint(s)
DAPT	20,645 12-month event-free	12 vs. 30 months	All DES (n 15,245), BMS (n 5,400)	1. Death/MI/stroke at 33 months 2. Definite/probable ST at 33 months	GUSTO bleeding
ISAR-SAFE	6,000 6-month event-free	6 vs. 12 months	All DES	Death/MI/stroke/TIMI major bleed at 15 months	Individual component end points, ARC ST
OPTIMIZE	3,120 non-STEMI	3 vs. 12 months	ZES	1-year death/MI/stroke/ TIMI major bleed	ARC ST, bleeding
ITALIC	3,200	6 vs. 12 months	EES	1-year D/MI/Stroke/TVR/ major bleed	2- and 3-year D/ MI/Stroke/TVR/ major bleed
SECURITY	4,000 non ACS non-STEMI	6 vs. 12 months	Second generation DES	Definite and/or probable ST occurring between 6 and 24 months	Composite of 24 months MACE

Taken from Kandzari *et al*. *JACC* 2009 and www.clinicaltrials.gov

Sigmund Silber

Discussion

R: Are the current guidelines [Europe and USA] obsolete?

S: Yes and no. The American guidelines are obsolete, but the European guidelines are not. Randomised trials (REAL-LATE/ZEST-LATE, PRODIGY, EXCELLENT) have shown that DAPT longer than six months has no advantage for the patient. However, we have no data on the benefits of less than six months of DAPT. So, I think the current recommendations from the European Society of Cardiology (ESC) guidelines 2005 and 2010 are still valid.

L: I agree. I think it is very difficult to change guidelines. We are involved in the SECURITY trial which is randomising patients to six- vs. 12-month DAPT with second generation drug-eluting stents. One of the challenges we have seen is that when we tell patients to stop at six months they go to their referring physician who makes them continue because they are still afraid. What happened in 2006 [Barcelona firestorm] really got on people's skins and caused a lot of unnecessary fear. Therefore, if we need to change the guidelines—particularly the US guidelines—it would be something really challenging. Doing studies with even shorter than six-month DAPT (maybe a one-month or a three-month DAPT study) makes sense scientifically but putting it into practice is very challenging.

R: Will the available evidence and ongoing studies provide us with enough information to rely on a six-month DAPT regimen?

L: I hope that the SECURITY and ISAR-SAFE studies, which are looking at six-month vs. 12-month DAPT, will provide us with sufficient data to be able to safely say to our patients, referring physicians and also people who make guidelines that six months of DAPT is sufficient with second generation drug-eluting stents.

R: If your patient has been implanted with an everolimus (Abbott Xience) or zotarolimus (Medtronic's Resolute Integrity) drug-eluting stent, would you be comfortable advising him/her to stop DAPT after six months?

A: Yes, if the patient does not have additional risks. If they are stable angina, non-insulin dependent diabetic patients, with one or two stents, I think it is very reasonable to recommend six months. The big question is whether we should discuss and add to the current guidelines a situation that we generally see in our daily practice: cases of surgery when we need to interrupt DAPT for some time and then prescribe it back. If I had that situation, based on the current data we have with the Resolute stent, it would be fine to stop

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One-month and three-month DAPT, is it feasible?

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DAPT after 30 days to intervene in a lower risk patient and then prescribe it back.

R: Suppose that your patient had to stop DAPT for two and a half months and nothing happens. Would you advice the patient to return to DAPT or just aspirin?

A: With the data we have so far, I would rather keep the patient on DAPT for at least two or three additional months to complete the six-month period. We cannot be misled by the message of a one-month period for Resolute we have now and the three-month DAPT for overall drug-eluting stents such as Xience as a formal recommendation. I think the main message that we have is: it is ok to stop if you have to.

L: Something else to reiterate is the difference between interruption and discontinuation. A lot of these data (Resolute and Xience) is based on interruption, which means stopping DAPT for a short period and then re-continuing. How will these data change my practice? I am not going to start prescribing one month or three months but when I get a phone call from a referring physician asking if he/she can stop DAPT due to surgery, knowing that the patient has a second generation drug-eluting stent, I will feel more comfortable saying yes. But as soon as the patient finishes the procedure, he/she needs to recontinue.

A: Another important question is whether we should advise the physician to stop one drug or both drugs and which one. This is a discussion with the surgeon as well, because some surgeons will feel comfortable keeping the patient on aspirin.

S: We address this in our analysis [RESOLUTE clinical programme] and in most patients only clopidrogel was stopped and aspirin was continued and the worst outcome was in the first four weeks. Stopping both drugs can be deadly. So we need to give a clear message of "do not stop within the first four weeks". Another interesting side result of this analysis is that we should be less strong with bridging because many people are afraid of bridging if discontinuation or interruption of DAPT is necessary. Some people are bridging with warfarin, which does not make any sense, or heparin. If the patient really has to stop DAPT for surgery we should get this operation in a hospital with a 24-hour/seven days a week ready cath lab. But if it is a cath lab in the hospital and we are feeling safe with the newer generation zotarolimus-eluting stent then we do not need to do any bridging.

R: There is an agreement with regards to six-month DAPT being very reasonable for patients implanted with a second generation DES. We have all agreed that more than 12 months, if not for specific situations, is not necessary. The point is that we are discussing less than six months and about three months; there is no question about one month. Is three-month DAPT something that should be considered in the near future to reduce DAPT duration even further?

A: We do need a randomised trial. In the next few months,we are going to have data from the OPTIMIZE trial that was conducted in Brazil and enrolled more than 3,000 patients treated with the Endeavor stent (Medtronic), and had three-month vs. 12-month DAPT. It was a prospective, well designed, properly conducted trial that will add to our evidence to say that with that particular stent it would be acceptable to stop DAPT and have a more formal recommendation. It is reassuring to see that most of the retrospective data that we have on three-month DAPT support the fact that if we have to interrupt

Flavio Ribichini

DAPT it is OK, depending on the situation. But, formally, I think it is too premature to prescribe three months.

S: I would call it level of evidence C, which is expert opinion. So I would give it a 1C or 2AC recommendation if you have to stop unplanned DAPT with newer generation drug-eluting stents.

L: To interrupt or to discontinue completely?

S: That is a difficult question. I would rather discontinue and go for six months because it is still in the guidelines. If you do something against the guidelines and if something happens just by coincidence, then you have to justify why you were working against them. In this case, if it is unplanned to stop I would do this and then I would go for six months. After six months, I would stop.

R: Will bioabsorbable scaffolds make an impact and change our daily practice with DAPT?

A: I do not think so. We can discuss late safety benefits of these new devices after one or two years when the absorbsion period is over and then we are not going to be left with the ghost of late thrombosis. We have to remember that these devices are going to be slightly bulkier than the current Xience and Resolute devices, so I think we might need at least six months of DAPT and again we are going to enjoy the benefit of fully bioabsorbable scaffolds perhaps after 12 months. In summary, I do not think there is going to be a dramatic change in the current guidelines with the bioabsorbable devices.

L: I would not be surprised if in a certain respect this is a step backwards in the sense that we will require longer periods of DAPT. We will start putting four, five or six scaffolds to reconstruct a vessel, without concerns about placing as many as we want or need, with the excuse that they will be gone in a year or two. In that kind of patient one should ask: "Would I be comfortable using DAPT for six months?" Probably not! So I would not be surprised if in this kind of patient we will have to prescribe longer DAPT duration.

S: I would say yes, but in 10 years from now. In 10 years we will have more flexible bioabsorbable scaffolds with thinner struts. The current scaffolds remind me of the very first Cypher and Taxus DES, with very stiff stent struts. In the future, what might happen is that it is going to be very tough for bioabsorbable scaffolds to beat the newer generation of metallic stents. The advantages of using bioabsorble scaffolds in the future are directed to the psychology of the patient. It would be very important for them to know that this is not an implant that is going to stay forever. Another advantage is that we could avoid unnecessary cardiac catheterisations because bioabsorbable scaffolds are more visible in cardiac CT than metallic stents.