Editorial

Long-term dual antiplatelet therapy and concomitant optimal medical therapy following percutaneous coronary intervention

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The dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor exerts protection against ischemic myocardial recurrences. During last two decades, DAPT has become the mainstay for treating patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), following the initial demonstration that DAPT was superior to anticoagulant therapy in these patients. Initially, and for many years, DAPT was prescribed for 2 to 6 months after PCI in important trials of stent implantation leading to the approval of early-generation drug-eluting stents (DES) by the US Food and Drug Administration. However, the subsequent increasing safety concerns related to the potential occurrence of late and very late stent thrombosis (ST) after implantation of early-generation DES lead to the recommendation of prolonging DAPT to 12 months by the American guidelines (1).

On this background, different studies have specifically investigated the comparison of different DAPT regimens after PCI and the optimal duration of DAPT still remains matter of discussion (2-9).

From one hand, some trials explored the effects of a short DAPT regimen (3 to 6 months) compared with 12 months DAPT supporting that such approach is as effective and safer being associated with similar ischemic events but reduced risk of bleeding. In patients with clinical characteristics such as to be considered at high bleeding risk, a 1-month DAPT was also found to be safe and effective after new-generation DES (10,11). On the other hand, other trials, consisting mainly of patients treated with elective DES implantation, compared prolonged DAPT (total therapy duration: 18 to 48 months) with 6 to 12 months of DAPT to determine whether extended therapy reduces late and very late stent thrombosis and prevents ischemic events associated with disease progression and plaque rupture at other nonstented sites. The majority of these trials (PRODIGY, ITALIC, DES-LATE, OPTIDUAL, ARCTIC Interruption) did not support the hypothesized benefits of DAPT prolongation, rather underlying concerns in terms of bleeding events (8,9,12). In contrast, the largest of these trials, the DAPT study, found that prolonging DAPT was associated with reduction of ischemic events, although this was mainly proven for the larger population of patients receiving DES implantation (n=9,961) rather than in those receiving a bare metal stent (n=1,687) (13,14). In the DAPT study, patients treated with DES or BMS implantation who received DAPT for 12 months and were without ischemic or bleeding events during this period were randomized to an additional 18 months of DAPT or to aspirin monotherapy. In the overall cohort and in the DES subgroup, extended DAPT resulted in a significant reduction in very late ST, myocardial infarction (MI), major adverse cardiac and cerebrovascular events (MACCE defined as death or MI or stroke), and increased risk of moderate or severe bleeding. In the patients receiving BMS, the DAPT prolongation did

not reduce significantly ischemic outcomes but increased bleeding events, however, it should be noted that there was no significant interaction between subgroups (DES and BMS) and the BMS subset may have been underpowered to identify such differences (14).

Some have hypothesized that "the longer, the better", however, this remains a matter of ongoing debate with many concerns on this approach. Indeed, a major issue that emerged from the DAPT study was the increase of non-cardiovascular mortality observed in patients prolonging DAPT and subsequently this was further confirmed in meta-analyses (5,8,9,13).

The large body of contrasting evidence accumulated during last years on the optimal duration of DAPT after stent implantation has led to growing discussion. Currently, the common consensus among opinion leaders is that there is no "*one size fits all*" approach and no common rule for the duration of DAPT after implantation of coronary stents (4,5,15). Consequently, a tailored approach may be advisable, wherein the personalized risks of ischemic versus bleeding events are carefully considered for each patient. A realistic estimation of the long-term ischemic and bleeding risk in each patient undergoing PCI is of paramount importance to tailor the optimal DAPT duration.

Accordingly, DAPT prolongation after the mandatory period seems to be more appropriate in patients at high risk for ischemic events but with relatively low risk of bleeding. In opposite, a 3- to 6-month DAPT regimen may be the ideal approach for patients with increased risk of bleeding based on the relatively high incidence of late bleeding events during DAPT therapy with harmful effect on survival. A shorter DAPT (i.e., 1-month) has been found to be safe and effective in patients with high risk of bleeding (i.e., elderly, need for oral anticoagulation, need for major noncardiac surgery, severe anemia, history of bleeding or transfusion, non-skin cancer, renal failure, severe liver disease, thrombocytopenia, planned long-term use of steroids or nonsteroidal anti-inflammatory drugs). Thus, there is a great interest in exploring specific clinical conditions that can identify patients in whom the benefit-risk ratio could be in favor or disfavor of DAPT continuation. Some subgroups have shown to benefit from extending DAPT due to their increased ischemic risk, such as patients with ACS at presentation (16), prior myocardial infarction (17), peripheral arterial disease (18) or those with multivessel disease or complex lesions (19,20). On the contrary, other conditions, such as diabetes (21), gender (22,23), chronic kidney disease (24), and elderly patients (25) did not emerge to be per se relevant drivers of the DAPT prolongation.

In line with the strategy to search for factors helping to individualize the optimal DAPT regimen patient-by-patient, Resor and colleagues recently investigated the impact of optimal medical therapy (OMT) on the treatment effect of DAPT (26). This analysis was conducted in the setting of all patients enrolled in the randomized DAPT study, including those treated with DES or BMS.

OMT was defined at the time of randomization as a combination of any dose statin, β-blocker, and ACE inhibitor/ARB use in patients with class I indication for each medication in agreement with American guidelines: (I) statin: all patients were considered to have an indication; (II) β-blocker: reduced ejection fraction, congestive heart failure, previous MI or ACS; (III) ACE inhibitor/ARB: hypertension, diabetes mellitus, reduced ejection fraction, or chronic kidney disease (26).

The overall finding of the study that DAPT prolongation provided ischemic benefits at the cost of increased bleeding was confirmed irrespective of OMT status, therefore, this analysis suggested that the decision to continue or interrupt DAPT beyond 12 months should not be based on the OMT.

OMT is recommended in patients with CAD due to the evidence of being associated with decrease of ischemic events and death. However, it is unknown whether the reduced risk in OMT patients may be also associated with a reduced or ischemic benefit related to prolongation of DAPT exposing thus the patient only to the increased bleeding risk related to such a strategy. The present subanalysis of the DAPT study seems to support the concept that there is no interaction between OMT and DAPT, rather suggesting that they may act synergistically through different mechanisms in order to reduce ischemic events (26). The authors also explored predictors of being or not on OMT and found that younger patients or those presenting with ACS or receiving clopidogrel instead of prasugrel were associated with higher rates of OMT. It is, however, an important concern that delicate categories such as patients with previous MI, previous PCI, renal insufficiency or hypertension more frequently were associated with lower rates of OMT. Although potentially interesting, these observations may have been related, at least in part, to different regional patterns of drug management, indeed, suboptimal OMT was mainly observed in North America compared with other sites.

The study is interesting, original, well conducted,

includes a large number of patients, and almost complete data on concomitant medication.

The findings, however, require some important considerations to allow an appropriate interpretation:

- First, the study was not prespecified and should be considered hypothesis-generating only;
- Second, OMT was a binary definition and the two groups (on OMT and off OMT) were attributed on the basis of therapy at enrollment, but OMT status is actually dynamic and in individual patients may have been modified throughout the study;
- Third, the definition of OMT status was performed without considering real reasons for not assuming a specific drug (contraindication, allergy, etc.) or taking into account lipid and blood pressure levels (did patients defined to be on OMT really reach the recommended targets for OMT?) or the dosage of drugs (i.e., this is particularly relevant for patients with reduced ejection fraction and indication to b-blockers);
- Fourth, the impact of OMT was only tested for the period of randomized treatment to DAPT versus aspirin alone between 18–30 months. In the DAPT analysis restricted to DES implantation, an important rebound effect was observed after DAPT interruption from 30 to 33 months and it would be interesting to know if OMT did not play a relevant role also in this phenomenon;
- Finally, there was a selective reporting of outcomes. Although mortality, stent thrombosis and stroke outcomes were included in the MACCE, they were not individually reported, thus a potential interaction of OMT status with these endpoints cannot be excluded. Especially in the DAPT study, all-cause mortality has emerged as an important and debated issue in the group of patients receiving DAPT prolongation and it would be interesting if this outcome had been reported. Indeed, we do not know whether OMT would have mitigated or not the increased risk of mortality described in those patients.

OMT represents a crucial but often underestimated aspect of post-procedural PCI care (26,27). The control of multiple cardiovascular risk factors decreases the incidence of cardiovascular events (27,28). OMT is a broad term that includes specific pharmacotherapy to control arterial hypertension, hyperlipidemia, and chronic hyperglycemia as well as the control of lifestyle risk factors (weight loss, smoking cessation, dietary regimen, exercise, and life rhythms). Importantly, the European Society of Cardiology guidelines highlighted that OMT should not be considered an alternative but a synergistic approach to revascularization (28).

In our opinion, from a practical point of view, the most relevant and also worrisome aspect emerged from this study, irrespective of DAPT regimen, and confirming other previous evidence, is the suboptimal frequency of OMT, indeed, approximately 37% of patients were not on OMT. Importantly, this appears to be even more alarming when we consider that the patients enrolled in the DAPT study represented a selected population of patients that were assumed to be at low risk of altered adherence to medical therapy; indeed, 12 months after PCI, only patients event-free and with appropriate compliance to thienopyridine therapy (defined as having taken 80% to 120% of the drug without stopping it for >14 days) were eligible for randomization. Although adherence to therapy was not assessed individually in each group, the overall good adherence of the enrolled patients to the medical treatment was confirmed by consistency of the rates of patients assuming statin, β-blocker, ACEi/ARB and OMT at randomization (12 months after PCI) and at end of the study (30 months after PCI). We may therefore assume that the rates of those without OMT in real practice might be much higher, which should raise a red flag for all practitioners. Notably, patients without OMT had higher rates of MI, MACCE and moderate or severe bleeding compared with patients on OMT. Therefore, given that the proportion of patients not on OMT still remains large, this study underlines a major unmet need in current practice: more and more organized efforts are needed to increase adherence and adherence awareness in our community and within our patients.

The real challenge in the 21-century seems to be finding ways to let the community apply established evidence even more than identifying new treatment venues.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:e574-651.
2. Valgimigli M, Ariotti S, Costa F. Duration of dual antiplatelet therapy after drug-eluting stent implantation: will we ever reach a consensus? Eur Heart J 2015;36:1219-22.
3. Valgimigli M, Costa F, Byrne R, et al. Dual antiplatelet therapy duration after coronary stenting in clinical practice: results of an EAPCI survey. EuroIntervention 2015;11:68-74.
4. Montalescot G, Brieger D, Dalby AJ, et al. Duration of Dual Antiplatelet Therapy After Coronary Stenting: A Review of the Evidence. J Am Coll Cardiol 2015;66:832-47.
5. Palmerini T, Stone GW. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: conceptual evolution based on emerging evidence. Eur Heart J 2016;37:353-64.
6. Capodanno D, Gargiulo G, Buccheri S, et al. Meta-Analyses of Dual Antiplatelet Therapy Following Drug-Eluting Stent Implantation: Do Bleeding and Stent Thrombosis Weigh Similar on Mortality? J Am Coll Cardiol 2015;66:1639-40.
7. Gargiulo G, Windecker S, Vranckx P, et al. A Critical Appraisal of Aspirin in Secondary Prevention: Is Less More? Circulation 2016;134:1881-1906.
8. Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. BMJ 2015;350:h1618.
9. Palmerini T, Benedetto U, Bacchi-Reggiani L, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet 2015;385:2371-82.
10. Ariotti S, Adamo M, Costa F, et al. Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?: A Pre-Specified Analysis From the ZEUS Trial. JACC Cardiovasc Interv 2016;9:426-36.
11. Urban P, Meredith IT, Abizaid A, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. N Engl J Med 2015;373:2038-47.
12. 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;125:2015-26.
13. 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;371:2155-66.
14. Kereiakes DJ, Yeh RW, Massaro JM, et al. Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: the dual antiplatelet therapy randomized clinical trial. JAMA 2015;313:1113-21.
15. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation 2016;134:e123-55.
16. Costa F, Vranckx P, Leonardi S, et al. Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial. Eur Heart J 2015;36:1242-51.
17. Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J 2016;37:390-9.
18. Franzone A, Piccolo R, Gargiulo G, et al. Prolonged vs Short Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With or Without Peripheral Arterial Disease: A Subgroup Analysis of the PRODIGY Randomized Clinical Trial. JAMA Cardiol 2016;1:795-803.

19. Lee SY, Hong MK, Shin DH, et al. Association Between Duration of Dual Antiplatelet Therapy and Angiographic Multivessel Disease on Outcomes in Patients Treated With Newer-Generation Drug-Eluting Stents. Circ Cardiovasc Interv 2016;9. pii: e004256.
20. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol 2016;68:1851-64.
21. Gargiulo G, Windecker S, da Costa BR, et al. Short term versus long term dual antiplatelet therapy after implantation of drug eluting stent in patients with or without diabetes: systematic review and meta-analysis of individual participant data from randomised trials. BMJ 2016;355:i5483.
22. Gargiulo G, Ariotti S, Santucci A, et al. Impact of Sex on 2-Year Clinical Outcomes in Patients Treated With 6-Month or 24-Month Dual-Antiplatelet Therapy Duration: A Pre-Specified Analysis From the PRODIGY Trial. JACC Cardiovasc Interv 2016;9:1780-9.
23. Sawaya FJ, Morice MC, Spaziano M, et al. Short-versus long-term Dual Antiplatelet therapy after drug-eluting stent implantation in women versus men: A sex-specific patient-level pooled-analysis of six randomized trials. Catheter Cardiovasc Interv 2017;89:178-89.
24. Gargiulo G, Santucci A, Piccolo R, et al. Impact of Chronic Kidney Disease on 2-Year Clinical Outcomes in Patients Treated with 6-Month or 24-Month DAPT Duration: An Analysis from the PRODIGY Trial. Catheter Cardiovasc Interv 2017. [Epub ahead of print].
25. Piccolo R, Magnani G, Ariotti S, et al. Ischemic and Bleeding Outcomes in Elderly Patients Undergoing a Prolonged versus Shortened Duration of Dual Antiplatelet Therapy after Percutaneous Coronary Intervention. Insights from the PRODIGY randomized trial. EuroIntervention 2017;13:78-86.
26. Resor CD, Nathan A, Kereiakes DJ, et al. Impact of Optimal Medical Therapy in the Dual Antiplatelet Therapy Study. Circulation 2016;134:989-98.
27. Iqbal J, Zhang YJ, Holmes DR, et al. Optimal medical therapy improves clinical outcomes in patients undergoing revascularization with percutaneous coronary intervention or coronary artery bypass grafting: insights from the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial at the 5-year follow-up. Circulation 2015;131:1269-77.
28. Task Force Members, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003

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